

**PORTLAND VETERANS AFFAIRS
MEDICAL CENTER**

INSTITUTIONAL REVIEW BOARD

Standard Operating Procedures

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TABLE OF CONTENTS

| | | | |
|-------------|-----------|------------|---|
| 3 | | | Introduction |
| 4 | | | Abbreviations |
| 5 | | | Definitions |
| I | BG | 100 | BACKGROUND |
| 12 | | 101 | Ethical Principles Governing the IRB |
| 13 | | 102 | The Regulatory Mandate to Protect Human Subjects |
| II | IA | 200 | INSTITUTIONAL REVIEW BOARD ADMINISTRATION |
| 14 | | 201 | Authority of the IRB |
| 15 | | 202 | Purpose of the IRB |
| 16 | | 203 | Review of Policies and Procedures |
| 17 | | 204 | Shared Responsibilities of the Institution in Protecting Human Subjects |
| III | OM | 300 | IRB ORGANIZATION AND MEMBERSHIP |
| 26 | | 301 | IRB Membership and Responsibilities |
| 31 | | 302 | Training of IRB Chairs and Members |
| IV | EI | 400 | EXEMPTION FROM IRB OVERSIGHT/REVIEW |
| 33 | | 401 | Exemption from IRB Oversight/Review |
| V | FO | 500 | FUNCTIONS AND OPERATIONS |
| 35 | | 501 | IRB Recordkeeping and Required Documentation |
| 44 | | 502 | IRB Meetings |
| 45 | | 503 | Use of Primary Reviewers with Convened IRB Reviews |
| 46 | | 504 | Materials for IRB Review |
| 49 | | 505 | Notifications of IRB Review |
| 51 | | 506 | Appeal of IRB Determinations |
| 52 | | 507 | Individualized IRB Consultations |
| 53 | | 508 | Audits of Research Protocols or Study Procedures |
| 54 | | 509 | Electronic Submission of Informed Consent Forms |
| VI | RR | 600 | ROUTINE IRB REVIEW |
| 55 | | 601 | Initial Review |
| 60 | | 602 | Ongoing Review |
| 68 | | 603 | Required Criteria For IRB Approval Of Research |
| 73 | | 604 | Additional Considerations During IRB Review and Approval of Research |
| 80 | | 605 | Review of Research Involving Potentially Vulnerable Populations |
| 84 | | 606 | Review of Research on Human Subjects Likely to Need Surrogate Consent |
| VII | EX | 700 | EXPEDITED IRB REVIEW of RESEARCH |
| 89 | | 701 | Expedited Review of Research |
| 90 | | 702 | Expedited Review of Minor Changes in Previously Approved Research |
| 91 | | 703 | Expedited Initial and Continuing Review: Permitted Categories |
| VIII | IC | 800 | INFORMED CONSENT |
| 94 | | 801 | Informed Consent Requirements and Documentation |
| 105 | | 802 | Exceptions from Informed Consent for Emergency Use of a Test Article |
| IX | SC | 900 | SPECIAL CONSIDERATIONS for SPECIAL TYPES of RESEARCH |
| 106 | | 901 | Behavioral and Social Sciences Research |
| 108 | | 902 | Research Using Data |
| 110 | | 903 | Epidemiological Research |

| | | | |
|-----------|-----------|-------------|--|
| 111 | | 904 | Family History Research |
| 112 | | 905 | Research Involving Potentially Addictive Substances |
| 113 | | 906 | Research Involving PVAMC Employees, Students and Trainees |
| 114 | | 907 | Human Fetal Tissue Transplantation Research |
| 115 | | 908 | Research Involving Deceased Persons |
| | | | |
| X | FD | 1000 | IRB MANAGEMENT OF FOOD AND DRUG ADMINISTRATION (FDA) REGULATED RESEARCH |
| 116 | | 1001 | Investigational Drugs, Devices, and Biologics |
| | | | |
| XI | AP | | APPENDICES |
| | | A | The Nuremberg Code, Declaration of Helsinki and Belmont Report |
| | | B | Federal Wide Assurance |
| | | C | IRB Forms – Website Reference |
| | | D | IRB Membership and Meeting Schedule |
| | | E | IRB Reviewer Forms |
| | | F | Adverse Event/Unanticipated Event Reporting Form |
| | | G | Applicable Oregon and Washington State Statutes |
| | | H | Informed Consent Templates and Checklists |
| | | I | IRB Coordinator Contact Information |
| | | J | HRPP: Policy & Procedure No. 2, Investigational Device Usage in R&D Service |
| | | K | HRPP: Policy & Procedure No. 3, Complaints and Allegations of Non-Compliance Pertaining to Human Research |
| | | L | HRPP: Policy & Procedure No. 4, Education for the Protection of Human Research Subjects |
| | | M | HRPP: Policy & Procedure No. 5, Conflict of Interest in Human Research |
| | | N | HRPP: Policy & Procedure No. 6, Health Insurance Portability & Accountability Act (HIPAA) Human Research Policies and Procedures |
| | | O | HRPP: Policy & Procedure No. 7, Policy for Determination of Institutional Review Board Review of Case Reports |
| | | P | HRPP: Policy & Procedure No. 8, Posting Recruitment Flyers at the PVAMC for Non-VA Research |
| | | Q | HRPP: Policy & Procedure No. 9, Continuous Quality Improvement in the Human Research Protection Program |
| | | R | HRPP: Policy & Procedure No. 10, Credentialing of Personnel Involved in Human Subjects Research |
| | | S | VHA Directive 2000-043: Banking of Human Research Subjects' Specimens |
| | | T | Humanitarian Use Device Information and Flowchart |
| | | U | Planned Emergency Research |

INTRODUCTION

The Portland VA Medical Center (PVAMC) Institutional Review Boards' (IRB) Standard Operating Procedures (SOP) for the protection of human subjects in research is a reference for IRB members, IRB Coordinators, investigators, and other individuals associated with the Human Research Protection Program (HRPP). This SOP details the policies and procedures specifying the regulations and policies governing human subjects research and the requirements for submitting research proposals for review by the IRB and the Research & Development Committee. All references to IRB in this document refer to both IRB#1 and IRB#2. Each IRB shall adhere to the policies and procedures outlined in this SOP.

Questions regarding the PVAMC IRB SOP may be directed to the:

IRB #1 Chair, IRB Coordinators, and the Research Assurance & Compliance Coordinator.

Additional information about the Research Program and the Human Research Protection Program may be found on the PVAMC Research & Development Home Page, accessed through the following link: <http://www.va.gov/portlandrd/>.

ABBREVIATIONS

| | |
|-------|---|
| ACOS | Associate Chief of Staff |
| AE | Adverse Event |
| AO | Administrative Officer |
| CFR | Code of Federal Regulations |
| COS | Chief of Staff |
| CRF | Case Report Form |
| CRQ | Continuing Review Questionnaire |
| CRADO | Chief Research and Development Officer |
| DHHS | Department of Health & Human Services |
| DPAHC | Durable Powers of Attorney for Health Care |
| DSMB | Data Safety Monitoring Board |
| FDA | Food and Drug Administration |
| FWA | Federalwide Assurance |
| HIPAA | Health Insurance Portability & Accountability Act |
| HRPP | Human Research Protection Program |
| ICF | Informed Consent Form |
| IDE | Investigational Device Exemption |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IRQ | Initial Review Questionnaire |
| MIRB | Manage Your Institutional Review Board |
| OHRP | Office for Human Research Protections |
| OHSU | Oregon Health & Sciences University |
| ORD | Office of Research and Development, VA Central Office |
| ORO | Office of Research Oversight |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PVAMC | Portland VA Medical Center |
| R&D | Research & Development |
| RACC | Research Assurance & Compliance Coordinator |
| RSO | Radiation Safety Officer |
| SAE | Serious Adverse Event/Experience |
| SOP | Standard Operating Procedures |
| UAE | Unexpected Adverse Event/Experience |

DEFINITIONS

- **Adverse event (AE):** (VHA Handbook 1200.5, July 15, 2003, (3.a.)) An AE is defined as any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research, or any risk associated with the research or the research intervention, or the assessment.
 - (1) **Serious Adverse Event/Experiences (SAE):** A SAE is defined as a life threatening experience; hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly and/or birth defects; an event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes; or death.
 - (2) **Unexpected Adverse Event/Experiences (UAE):** An UAE is any adverse event and/or reaction, the specificity or severity of which is not consistent with the informed consent, current investigator brochure or product labeling. Further, it is not consistent with the risk information described in the general investigational plan or proposal.
- **Administrative termination:** projects whose approval period has expired and the Principal Investigator (PI) has failed to complete the continuing review paperwork (provided there are no subjects currently enrolled) may be administratively terminated at the discretion of the IRB. In such a case the PI will be notified of the termination and a new submission will be required if the project is to resume.
- **Administrative Withdrawal:** a new proposal that has received contingent approval or was tabled at the IRB initial review may be administratively withdrawn if the PI fails to meet the contingencies the IRB has specified. Please see Section VI, RR, 601, C for more information. In such a case the PI will be notified of the withdrawal and a new submission will be required if the project is to resume.
- **Anonymous Research:** Scientific or medical research conducted in such a manner that the identity of an individual who has provided a sample, or the identity of an individual from whom genetic information has been obtained, or the identity of the individual's blood relatives cannot be determined. "Anonymous research" does not include research conducted in such a manner that the identity of such an individual, or the identity of the individual's blood relatives, can be determined by the use of a code, encryption key or other means of linking the information to a specific individual.
- **Blinded:** (VHA Handbook 1200.5, July 15, 2003, (3.c.)) A study design comparing two or more interventions in which the investigators, the subjects, or some combination thereof, do not know the treatment group assignments of individual subjects; it is sometimes called a masked study design.
- **Conflict of Interest:** A conflict of interest exists when an individual's financial interests or other

obligations interfere, or appear to interfere, with the individual's obligations to act in the best interest of the human research participants and the PVAMC and without improper bias. This may include both financial and non-financial conflicts of interest. The mere appearance of a conflict may be as serious and potentially damaging to the public trust as an actual conflict. Therefore, potential conflicts must be disclosed, evaluated, and managed with the same thoroughness as actual conflicts. Please see the HRPP Policy & Procedure No. 5, Conflict of Interest in Human Research.

- **De-Identified**: De-identified information is health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual. In order to be considered de-identified, the following 18 elements must be removed: name; address; names of relatives; names of employers; birth date; telephone number; fax number; e-mail addresses; social security number; medical record number; health plan beneficiary number; account number; certificate/license number; any vehicle or device serial number; web URL; Internet Protocol Address; Finger or voice prints; Photographic images (e.g. full facial photographs); and any other unique identifying number, characteristic, or code. Information may also be statistically de-identified. This is typically performed by an experienced statistician who analyzes the data and affirms that the risk is "very small" that a particular person could be identified from the information collected.
- **Delivery**: means complete separation of the fetus from the woman by expulsion, extraction, or any other means.
- **Exempt Research**: (VHA Handbook 1200.5, July 15, 2003, (3.d.)) Exempt research is research determined by the Institutional Review Board (IRB) to involve human subjects only in one or more of certain minimal risk categories (38 CFR 16.101(b)). **NOTE**: Refer to Section IV, EI, 401, for a detailed description of the minimal risk categories.
- **Fetus**: is the product of conception from the time of implantation until delivery.
 - **Viable fetus**: is now termed a "viable neonate."
 - **Nonviable fetus**: is a fetus ex utero that, although living, is not able to survive to the point of independently maintaining heart and respiration. **NOTE**: *In 45 CFR 46 Subpart B, this definition is used as the definition of a non-viable neonate.*
 - **Dead fetus**: is a fetus which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord if still attached.
- **Human Biological Specimens**: are defined in the VHA Directive 2000-043 as "any material derived from human subjects, such as blood, urine, tissues, organs, hair, nail clippings, or any other cells or fluids, whether collected for research purposes or as residual specimens from diagnostic, therapeutic, or surgical procedures."
- **Human Research Protection Program (HRPP)**: (VHA Handbook 1200.5, July 15, 2003, (3.f.)) An HRPP is a comprehensive system to ensure the protection of human subjects participating in research. The ethical conduct of research is a shared responsibility among all individuals involved in the HRPP. It requires cooperation, collaboration, and trust among the institution, investigators and their staff, the subjects who enroll in the research, Institutional Review Board members, R&D Committee members, and R&D Service staff.

- **Human Subjects:** are defined by the federal regulations [38 CFR 16.102 (f)] as "living individual(s) about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information." As required by 38 CFR 16.102 (f) an intervention includes all physical procedures by which data are gathered and all physical, psychological, or environmental manipulations that are performed for research purposes. **The FDA regulations** [21CFR56.102(e)] also define a human subject as "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient."
The VA regulations definition of human subjects includes investigators, technicians, and other assisting investigators, when they serve in a "subject" role by being observed, manipulated, or sampled.
- **Individually-identifiable Information:** (VHA Handbook 1605.1, December 31, 2002) is any information, including health information maintained by VHA, pertaining to an individual that also identifies the individual and, except for individually-identifiable health information, is retrieved by the individual's name or other unique identifier. Individually-identifiable health information is covered by the Health Insurance Portability and Accountability Act of 1996 (HIPAA), regardless of whether or not the information is retrieved by name. This includes information of the individual which is or may be readily ascertained by the investigator or associated with the information, even through the use of a codebook. Typically, "individually identifiable information" is considered to be information that is attached to one or more unique identifiers. The 18 unique identifiers defined through HIPAA are in the HRPP Policy and Procedure No. 6. These include: patient's name, social security number, address, telephone number, etc.
- **Individually-identifiable Health Information:** (VHA Handbook 1605.1, December 31, 2002) is a subset of health information, including demographic information collected from an individual, that is: 1) created or received by a health care provider, health plan or health care clearinghouse; 2) relates to the past, present, or future condition of an individual and provision of or payment for health care; and 3) identifies the individual or a reasonable basis exists to believe the information can be used to identify the individual.
- **Institutional Review Board (IRB):** The IRB is a formally established subcommittee of the Research and Development (R&D) Committee with and for the purposes expressed in the Common Rule (38 CFR 16.102 (g)) and VHA Handbook 1200.5, July 15, 2003, (3.p.). The IRB, also known as the Subcommittee on Human Studies, is an appropriately constituted group that the VA has formally designated to review and monitor research involving human subjects to protect the rights and welfare of the subjects. The IRB also provides oversight and monitoring of such protections. In accordance with the Common Rule, VA and FDA regulations, the IRB has responsibility for approving, requiring modification (to secure approval), or disapproving research.
- **Investigational Device:** As defined by the FDA, an investigational device is a device that is the object of a clinical study designed to evaluate the safety or effectiveness of the device (21 CFR 812.3(g)). Investigational devices include transitional devices (21 CFR 812.3(r)) that are objects of investigations. According to the VHA Handbook 1200.5, July 15, 2003, (3.j), an investigational device may be an approved device that is being studied for an unapproved use or efficacy.
- **Investigational Drug:** (VHA Handbook 1200.5, July 15, 2003, (3.k.)) An investigational drug is a drug or biological drug that is used in a clinical investigation. The FDA considers the term

"Investigational New Drug (IND)" synonymous with investigational drug (21 CFR 312.3).

However, for purposes of this IRB SOP, an Investigational Drug may be an approved drug that is being studied for an unapproved or approved use in a controlled, randomized or blinded clinical trial.

- **Investigational Device Exemption (IDE):** (VHA Handbook 1200.5, July 15, 2003, (3.1.)) An IDE is an FDA-approval of the application for an exemption that permits an un-marketed device to be shipped for the purpose of doing research on the device. **NOTE:** See 21 CFR 812.1 and 812.2 for scope and applicability.
- **Investigational New Drug (IND):** (VHA Handbook 1200.5, July 15, 2003, (3.m.)) An IND is used to refer to either an investigational new drug application or to a new drug that is used in clinical investigations. IND is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." **NOTE:** See 21 CFR 312.2(a)-(b) for applicability and exemptions.
- **Investigator:** (VHA Handbook 1200.5, July 15, 2003, (3.n.)) An investigator is an individual under the direction of the Principal Investigator (PI) who is involved in some or all aspects of the research project, including the: design of the study, conduct of the study, analysis and interpretation of the collected data, and writing of resulting manuscripts. An investigator must be either compensated by VA, be appointed to work without compensation (WOC), or may be an employee assigned to VA through the Intergovernmental Personnel Act (IPA) of 1970. The FDA considers an investigator and a PI to be synonymous.
- **In vitro fertilization:** is any fertilization of human ova, which occurs outside the body of a female, either through a mixture of donor human sperm and ova or by any other means.
- **Ionizing Radiation:** (VHA Handbook 1200.5, July 15, 2003, (3.o.)) Ionizing radiation is particles or rays with sufficient energy to cause the ejection of orbital electrons from absorber atoms. Ionizing radiation should be addressed within the protocol and the informed consent when its use is part of the research study. Ionizing radiation includes diagnostic and therapeutic procedures done for research purposes. Sources of radiation include: nuclear medicine, radiation therapy, and radiology.
- **Legally Authorized Representative:** (VHA Handbook 1200.5, July 15, 2003, (3.q.), Oregon Revised Statutes 127.635(2), Washington State law RCW7.70.065) A legally authorized representative is defined as an individual, or judicial or other body, authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research in the following descending order of priority:
 - a. A "legally authorized representative" includes not only persons appointed as healthcare agents under Durable Powers of Attorney for Health Care (DPAHC)
 - b. Court appointed guardians of the person
 - c. Spouse
 - d. A majority of the adult children (18 years of age or older) who can be so located
 - e. Parent
 - f. A majority of the adult siblings (18 years of age or older) who can be so located

- **Minimal Risk:** (38CFR16.102(i)) a risk is minimal when the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- **Minors (Children):** are persons who have not attained the legal age of 18 for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.
- **Neonate:** means newborn.
 - **Viable neonate:** means being able, after delivery, to survive to the point of being independently maintaining heart and respiration (given the benefit of available medical therapy).
 - **Non-viable neonate:** means the same as a non-viable fetus.
- **Office of Research and Development (ORD):** (VHA Handbook 1200.5, July 15, 2003, (3.r.)) ORD is the office within VA Central Office responsible for the overall policy, planning, coordination, and direction of research activities within VHA. **NOTE:** The Program for Research Integrity Development and Education Program (PRIDE) is the program within ORD that is responsible for training, education, and policy development related to human subjects protection.
- **Office of Research Oversight (ORO):** (VHA Handbook 1200.5, July 15, 2003, (3.s.)) ORO is the primary VHA office for advising the Under Secretary for Health on all matters regarding compliance and oversight of research in the protection of human subjects, animal welfare, and research safety. ORO oversees investigations of allegations of research misconduct.
- **Pregnancy:** is the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.
- **Principal Investigator (PI):** (VHA Handbook 1200.5, July 15, 2003, (3.t.)) Within VA, a PI is an individual who conducts a research investigation, i.e., under whose immediate direction research is conducted, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. The FDA considers a PI and an investigator to be synonymous.
- **Prisoner:** is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.
- **Private Information:** information that an individual can reasonably expect will not be made public, and information about behavior that an individual can reasonably expect will not be observed or recorded. Private information is information about a patient and/or study participant that is “individually identifiable.” Please see the definition for “identifiable” above.
- **Qualified Designee:** a qualified designee for the IRB Chair is either the IRB Alternate Chair or other voting IRB member with commensurate experience.

- **Quorum:** (VHA Handbook 1200.5, July 15, 2003, (3.o.)) more than half of the voting members of a committee being present and including at least one member whose primary concerns are in non-scientific areas. At meetings of the IRB, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting.
- **Research:** is defined by the VA Federal regulations (38 CFR 16.102 (d)) as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

The VHA Handbook 1200.5, July 15, 2003, (3.v), defines research as the testing of concepts by the scientific method of formulating a hypothesis or research question, systematically collecting and recording relevant data, and interpreting the results in terms of the hypothesis or question.

The FDA regulations at 21CFR56.102(c), define research as "...any experiment that involves a test article and one or more human subjects..." The FDA regulations further state that "...the terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part."

The Portland VA Medical Center Medical Staff Bylaws define research as an activity designed to develop or contribute to generalizable knowledge through a process of hypothesis testing or data collection that permits conclusions to be drawn. Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective. Any prospective or retrospective collection of clinical data with the intent to contribute to generalizable knowledge constitutes human studies research. Examples of such clinical data collection include research seminars, posters, abstracts, manuscripts, and pilot data. Local medical center and affiliated institutional conferences for teaching, quality assurance or quality improvement activities, and patient care activities (for example, ward rounds, case conferences, departmental seminars, morbidity & mortality conferences, X-ray conferences, tumor boards) are specifically not considered as research by this definition. Case Reports (published reviews of 3 or less clinical records by one or more members of the care team) are not considered as research, but do require submission of a Case Report Review application to the IRB Coordinator. Clinical reviews (reviews of 4 or more clinical records whether or not care team members are involved) are considered human research and must have IRB and Research & Development Committee approval.

Questions regarding whether or not an activity is considered human subjects research should be directed to an IRB Coordinator.

Please also refer to Medical Center Memorandum (MCM) No. 151-01.

- **Research Records:** (VHA Handbook 1200.5, July 15, 2003, (3.w.)) Research records consist of IRB records as well as case histories (also referred to as investigator's research records) or any data gathered for research purposes.
 - (1) **IRB Records.** IRB records include but are not limited to: all minutes of IRB meetings, a copy of all proposals reviewed including all amendments, investigator brochures, any supplemental information including recruitment and informational materials, consent forms, information submitted for continuing review, all correspondence, and IRB membership with a resume for each member.

(2) **Case History.** A case history is a record of all observations and other data pertinent to the investigation on each research subject. An investigator is required to prepare and maintain adequate and accurate case histories. Case histories include the case report forms and supporting data including signed and dated consent forms, any medical records including, but are not limited to: progress notes of the physician, the individual's hospital chart(s), and nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.

- **Researcher:** (VHA Handbook 1200.5, July 15, 2003, (3.x.)) A researcher is the PI and/or investigator.
- **Suspension:** suspension of approval occurs when the IRB orders the research to stop pending an action (such as an investigation into the causes of adverse outcomes or a change to the protocol to further reduce a particular risk).
- **Termination:** termination of approval occurs when the IRB determines that the research study must cease.
- **Test Article:** (VHA Handbook 1200.5, July 15, 2003, (3.y.)) For purposes of this SOP, a test article is a drug, device, or other article including a biological product used in clinical investigations involving human subjects or their specimens.
- **VA-approved Research:** (VHA Handbook 1200.5, July 15, 2003, (3.z.)) VA-approved research is research that has been approved by the VA R&D Committee.

BG 101

Ethical Principles Governing the IRB

VA Research must be carried out in an ethical manner (38CFR16.103(b)(1)). The basic ethical principles governing research involving human subjects are provided in the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report, which are located in Appendix A.

A. The Nuremberg Code

The modern history of human subject protections begins with the discovery after World War II of numerous atrocities committed by Nazi doctors in war-related human research experiments. The Nuremberg Military Tribunal developed ten principles as a means of judging their “research” practices, known as *The Nuremberg Code*. The significance of the Code is that it addresses the necessity of requiring the voluntary consent of the human subject and that any individual “who initiates, directs, or engages in the experiment” must bear personal responsibility for ensuring the quality of consent.

B. The Declaration of Helsinki

Similar principles to The Nuremberg Code have been articulated and expanded in later codes, such as the World Medical Association *Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects* (1964, revised 1975, 1983, 1989, 1996, 2000), which call for prior approval and ongoing monitoring of research by independent ethical review committees.

C. The Belmont Report

The Belmont Report contains three basic ethical principles that are central to research involving human research and guide the IRB in assuring that the rights and welfare of subjects are protected. These three principles are:

1. **Respect for persons**, which is applied by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
2. **Beneficence** is applied so that possible benefits are maximized and possible risks are minimized to the persons involved.
3. **Justice** is evidenced in the equitable selection of subjects.

BG 102**The Regulatory Mandate to Protect Human Subjects**

The Department of Veterans Affairs (VA) and other Federal regulations require specific protections for human subjects:

A. Department of Health and Human Services (DHHS) Regulations at 45CFR46

In January 1991 the VA joined 16 other Executive Branch Departments and Agencies in simultaneously adopting the Federal Policy (Common Rule) for the Protection of Human Subjects. Codified by the VA at 38CFR16, the Common Rule is also codified by the Department of Health and Human Services (DHHS) as Subpart A of the DHHS regulations at 45CFR46. DHHS has three additional Subparts in the regulations, as well, that are not in 38CFR16. All human subject research conducted at the PVAMC must adhere to the regulations at 45CFR46 and 38CFR16.

B. VA regulations at 38 CFR 16 and the Federal Policy (Common Rule) for the Protection of Human Subjects

1. 38CFR16 – Protection of Human Subjects
2. 38CFR17.33 - Patients' rights
3. 38CFR17.85 - Treatment of research related injuries to human subjects
4. 38CFR17.45 - Hospital care in research studies
5. 38CFR17.92 - Outpatient care for research studies

Codified by the VA at 38 CFR 16, the Common Rule is identical to Subpart A of the DHHS regulations, but does not include the additional DHHS Subparts B, C, and D.

C Food and Drug Administration (FDA) Regulations

The following FDA regulations must also be adhered to when appropriate:

1. 21CFR50 – Protection of Human Subjects
2. 21CFR56 – Institutional Review Boards
3. 21CFR54 – Financial Disclosure by Clinical Investigators
4. 21CFR312 - Investigational New Drugs (IND)
5. 21CFR812 – Investigational Device Exemptions (IDE)

D. DHHS Office for Human Research Protections (OHRP) – Federalwide Assurance

DHHS mandates that every institution conducting human research with federal funds register itself with OHRP and obtain an assurance of compliance approved by the OHRP. Under this OHRP issued Federalwide Assurance (FWA), the IRB that reviews the human research projects is responsible for adhering to and fulfilling the requirements of the Federal regulations of 45CFR46.

A signed copy of the PVAMC FWA may be found in Appendix B. The Portland VAMC IRBs, abide by the terms set forth in the FWA.

The PVAMC IRB Assurance number is: FWA00000517.

The VA Med Ctr, Portland, OR IRB#1 Registration number is: IRB00001976.

The VA Med Ctr, Portland, OR IRB#2 Registration number is: IRB00003313.

The Community Based Outpatient Clinics identified for this assurance include: Bend, Camp Rilea, Longview, and Salem.

IA 201

The Authority of the IRB

(38 CFR 16; 21 CFR 50, 56; and 45 CFR 46)

A. PVAMC IRBs

The PVAMC IRBs, designated by the PVAMC Director and the R&D Committee (M-3, Part 1, Chapter 2.02 and 3.01), and named in the Federalwide Assurance (FWA) must prospectively review and make a decision concerning all human subject research conducted at the PVAMC or by PVAMC employees or agents, or otherwise under the auspices of the VA. Further, these IRBs have statutory authority to:

1. take any action necessary to protect the rights and welfare of human subjects in the research program;
2. approve, require modifications in, or disapprove the facility's human subjects research;
3. conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (38 CFR 16.109);
4. suspend or terminate the enrollment and/or ongoing involvement of human subjects in each facility's research as it determines necessary for the protection of those subjects (38 CFR 16.113); and
5. observe and/or monitor the PVAMC's human subject research to whatever extent it considers necessary to protect human subjects.

B. Other Institutions

The IRB is responsible for the protection of the rights and welfare of human research subjects at the PVAMC and for research conducted under PVAMC auspices.

The IRB may be designated for review of research under another institution's assurance only with the written agreement of the Medical Center Director and in accordance with applicable ORD and OHRP requirements. Any such designation must be accompanied by a written agreement specifying the responsibilities of the facility and its IRB under the other institution's assurance. IRBs operated by the PVAMC have no authority over, or responsibility for, research conducted at other institutions in the absence of such a written agreement.

IA 202

Purpose of the IRB (38 CFR 16.109)

The PVAMC IRBs' primary responsibility is to ensure that the rights and welfare of subjects are protected in the VAMC human subject research program (38 CFR 16.109). In doing so, the IRBs must ensure that the human subjects research is conducted ethically, and in compliance with VA, other Federal regulations, the requirements of applicable Oregon and Washington state laws, the signed Federalwide Assurance (FWA), and the PVAMC's institutional policies and procedures. The IRBs accomplish prospective and continuing review of the PVAMC's human subject research projects. This includes, but is not limited to, review of the protocol, the informed consent process, and all of the procedures used to enroll subjects.

The review process consists of a review at study inception, and at intervals appropriate to the degree of risk, but not less than once a year.

IA 203

Review of Policies and Procedures

This Standard Operating Procedure Manual of the IRB must remain current and in compliance with all applicable regulations. To remain current, this SOP Manual must be reviewed and periodically updated. The Research Assurance & Compliance Coordinator (RACC) with the assistance of the IRB Chairpersons, IRB Coordinators, ACOS/R&D, and AO/R&D will update these policies and procedures to comply with the most recent VA and federal regulations. Proposed changes will be presented to the IRB for input. Revisions will be implemented upon review and approval of a majority of the IRB. The revised version will then be forwarded to R&D Committee for approval. Notifications of changes and an updated SOP Manual will be distributed to members as appropriate.

Other documents used by the IRB for its day-to-day functions, including but not limited to investigator submission forms, investigator's manual, guidance documents, reviewer forms, and checklists, etc. will also be reviewed and revised as needed.

IA 204**Shared Responsibilities of the Institution in Protecting Human Subjects**

Although the IRB is a subcommittee of the R&D Committee (M-3, Part 1, Chapter 2.02, 3.01), neither the Medical Center Director nor the designated R&D Committee can approve research involving human subjects that has not been approved by the IRB of record (38 CFR 116.112; M-3, Part 1, Chapter 3.01(e)), nor can it alter an adverse report or recommendation made by the IRB. For example, the disapproval for ethical or legal reasons made by the IRB could not be reversed by the Medical Center Director or R&D Committee.

A. Medical Center Director

(38 CFR 16.112; M-3, Part 1, Chapter 2.02 and 3.01, MCM No. 151-01)

The **Medical Center Director** is the Federalwide Assurance Signatory Official. The Signatory Official is the official legally authorized to represent the institution under the Department of Health & Human Services approved Federalwide Assurance. The Medical Center Director is responsible for ensuring compliance with all Federal and VA regulations governing research and is accountable for the HRPP including the protection of human research subjects within the facility. The Director appoints the chairs and members of the R&D Committee and all of its subcommittees and reviews and approves all R&D Committee meeting minutes. (M-3, Part I, Chapter 2.02(a)).

The Director delegates the authority to administer the R&D program to the Associate Chief of Staff/R&D.

B. Chief of Staff

(MCM No. 151-01)

The Chief of Staff (COS) at PVAMC reports to the Medical Center Director and has overall responsibility for all clinical activities under the purview of the PVAMC.

C. Associate Chief of Staff/Research & Development (ACOS/R&D)

(MCM No. 151-01)

The **Associate Chief of Staff for Research & Development** reports to the Director through the COS and is responsible for:

1. Developing, managing and evaluating policies and procedures that ensure compliance with all state and Federal regulations governing research. This includes monitoring changes in state, VA and other Federal regulations and policies that relate to human research protection and overseeing all aspects of the HRPP program established for human research protections.
2. Acting as liaison between the VHA Office of Research and Development and the institution's R&D Committee, as well as advising the Director and VISN 20 leadership on key matters regarding research.
3. Implementing the institution's HRPP policy.
4. Submitting, implementing, and maintaining an approved FWA through the Medical Center Director and the Office of Research Oversight (ORO) and to the Department of Health & Human Services, (OHRP).

5. Administering the facility's R&D Programs, including the R&D Committee and applicable subcommittees.
6. Managing the finances of the facility's R&D Program.
7. Assisting investigators in their efforts to carry out VA's research mission.
8. Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate for the purpose of managing risk in the research program.
9. Developing training requirements and ensuring that these training requirements, including human, animal, and bio-safety research for investigators and members of the applicable subcommittees and staff are completed.
10. Fulfilling all other responsibilities and adhering to the policies and procedures as outlined in the appropriate institutional, HRPP, and R&D Service committee's policies and procedures.

D. Research & Development Committee

(M-3, Part I, Chapter 3.01, MCM No. 151-01)

The **Research & Development Committee** serves in an advisory capacity to the Medical Center Director through the COS on the professional and administrative aspects of the research program. This oversight includes the assessment of scientific quality of research and development projects and protection of human research subjects. The R&D Committee is responsible for:

1. Assuring the continuing quality of the facility's R&D program.
2. Planning and developing broad objectives of the R&D program so that it supports the patient care mission of the facility.
3. Evaluating critically and deciding approval/disapproval of research with respect to the:
 - (a) Quality, design, desirability and feasibility of each new R&D proposal;
 - (b) Continuing R&D projects;
 - (c) Application for funding;
 - (d) Manuscripts to be submitted for publication; and
 - (e) Other reporting activities to assure maintenance of high scientific standards, protection of human subjects, adequate safety measures and proper use of animal subjects.
4. Reviewing and declaring approval/disapproval recommendations from its subcommittees:
 - (a) Institutional Review Board (IRB);
 - (b) Institutional Animal Care and Use Committee (IACUC);
 - (c) Subcommittee on Research Safety (SRS); and
 - (d) Subcommittee on Research Space.
 - (e) The R&D Committee will not approve any proposal that has been disapproved by any subcommittee, nor will it alter any documents or recommendations made by any subcommittees.
5. Recommending the distribution of R&D funds, space, personnel, equipment, supplies, use of animal facilities and other common resources on the basis of such evaluations and after consideration of other needs. This includes an annual review of the budget assigned to the HRPP.
6. Reviewing on an annual basis the subcommittees' Chair and members and the members' qualifications and experiences. These subcommittees include the IRB, IACUC, SRS and Subcommittee on Research Space.
7. Reviewing, evaluating, and as needed, recommending appropriate corrective actions, regarding the reports and results of compliance assessment and quality improvement activities (QA/QI) related to research.

8. Reviewing and declaring approval/disapproval of new and revised HRPP policies and procedures.
9. Evaluating, annually, investigator compliance with HRPP and IRB requirements.
10. Fulfilling all other responsibilities and adhering to the policies and procedures as outlined in the appropriate institutional, HRPP, and R&D Service committee's policies and procedures.
11. Reviewing all disclosed conflicts of interest in human research identified by the IRQ or identified otherwise during IRB review.

As stated in the R&D Committee SOP, the R&D Committee adheres to these procedures:

All study protocols which have been reviewed and approved by the IRB, must also be reviewed and approved by the R&D Committee, prior to study initiation. The R&D Committee is notified in writing of the IRB decisions regarding each protocol through the IRB meeting minutes, which are submitted to and reviewed by the R&D Committee. The R&D Committee also re-evaluates at least annually the scientific quality of all research studies involving human subjects to assure protection of human subjects.

If in the course of its review, the R&D Committee requires changes to a protocol, including those that relate to the determination of the protection of human subjects, the R&D Committee must refer those changes back to the appropriate subcommittee for its approval before the R&D Committee can give final approval.

In addition, the R&D also reviews and evaluates reports and results of compliance assessment and quality improvement activities.

The MCM No. 151-01, R&D Committee's Standard Operating Procedures, and Human Research Protection Program (HRPP) policies and procedures provide additional information regarding the responsibilities, functions, and procedures of the R&D Committee.

The R&D Committee has charged the PVAMC **Institutional Review Boards** (IRB) with the oversight of all research activities involving the use of human subjects. The PVAMC IRBs shall perform all of the functions required under 38 CFR 16 (Common Rule) for reviewing and approving human subjects research conducted under the auspices of the Institution's FWA. This includes, but is not limited to, research supported by the VA or conducted at the PVAMC, except as outlined in MCM No. 151-01, and research involving VA patients as research subjects (hereafter "VA research"). These responsibilities include maintaining the assurances of compliance set forth in the FWA obtained from the OHRP and only approving research involving human research subjects in accordance with all applicable federal requirements in the protection of human research subjects and operations of the IRB. IRB review and approval of VA Research shall be conducted in accordance with 38 CFR 16, 45 CFR 46 Subparts A through D, 21 CFR 50 and 56 (where applicable), and all relevant academic affiliate policies and VA rules and policies set forth in writing in VA policy M-3, Part I, Ch. 9, and Handbooks as developed.

E. Administrative Officer/Research & Development (AO/R&D)

The Administrative Officer (AO) conducts the administrative pre-review of all studies proposed for review by the IRB. The AO must review and approve proposed research projects to assure appropriate facility resources and appropriateness of conducting the study at the PVAMC. This process is achieved through the AO review of the IRB submission requirements completed by the principal

investigator. The PI must submit the Proposed Project Questionnaire (PPQ) with all applicable attachments to the IRB Coordinators by the 20th of each month. Once the administrative review is complete, the research project may be reviewed by one of the PVAMC IRBs. By signing the "Proposed Project Questionnaire," the AO/R&D acknowledges the resources involved and appropriateness of performing the study at the PVAMC. **Studies which are not approved during the AO review will not be reviewed by the R&D Committee and will not be conducted at the PVAMC.**

In addition, the AO serves as an ex-officio member of the IRB.

F. **The Principal Investigator**

(VHA Handbook 1200.5, (10), M-3, Part 1, Chapter 9.11 & Appendix C, PVAMC MCM No. 151-01)

The IRB recognizes one Principal Investigator (PI) for each project. If the Principal Investigator does not have a VA appointment, then a VA responsible individual is identified on the research project proposal and serves as the Principal Investigator for the study at the PVAMC. The VA Responsible Investigator is responsible for the conduct of the study at the PVAMC and must adhere to the PI responsibilities. All PI have the responsibility to submit proposed research involving human subjects for approval or exemption from IRB review.

The PI has ultimate responsibility for his/her research project. The PI has obligations and duties to act in accordance with the policies of the HRPP and the IRB and to report to the IRB as required. The PI is notified in writing of IRB decisions regarding each protocol. All official IRB correspondence is addressed to the PI, but may be sent to a Study Coordinator as designated by the PI on the Initial Review Questionnaire. In cases where a lapse in time could potentially harm human subjects (such as in the report of an adverse event), Co-Investigators may communicate directly with the IRB.

1. The **Principal Investigators** (VA, Without Compensation or contract employees) who are planning to conduct human studies research at the PVAMC are responsible for adhering to the responsibilities, policies and procedures outlined in the MCM No. 151-01, IRB SOP and HRPP policies and procedures.
2. The **Principal Investigators** who are planning to conduct research at the PVAMC are responsible for:
 - (a) Submitting the following applicable forms to the Administrative Officer of R&D Service in a timely manner prior to submitting a research proposal to a funding agency:
 - (1) Proposed Project Questionnaire (PPQ);
 - (2) Administrative Review forms;
 - (3) Project Proposal (protocol) and Abstract;
 - (4) Institutional Review Board forms;
 - (5) Institutional Animal Care and Use Committee forms; and
 - (6) Subcommittee on Research Safety forms.These forms may be obtained from the R&D Service website:
<http://www.va.gov/portlandrd/pages/support/award/form.htm>
 - (b) Submitting annual and continuing reviews of the research project to the R&D Service administrative office according to stated deadlines for entry into the Research & Development Information System (RDIS) database. All required reports will be

- submitted by the due date(s) specified by the R&D Service administrative office to comply with Federal, VACO and local requirements.
- (c) Completing educational requirements, educating their staff and monitoring all safety rules and regulations in their laboratory including the requirements for annual safety training. Compliance with all requirements of the Subcommittee on Research Safety is the responsibility of each employee.
 - (d) Submitting publications that result from this research to the R&D Committee for approval prior to publication. The publication must include the PVAMC in the address of authors and VA support must be mentioned in a footnote or acknowledgment.
 - (e) Fulfilling all other responsibilities and adhering to the policies and procedures as outlined in the appropriate institutional, HRPP, and R&D Service committee's policies and procedures.
3. For **research involving human subjects** at the PVAMC, the Principal Investigator must adhere to the following procedures:
- (a) Complete all required education in the protection of human research participants.
 - (b) Maintain credentials and privileges at the PVAMC appropriate for performing all procedures proposed in all research protocols involving human subjects submitted by the principal investigator. If the principal investigator lacks the requisite credentials and privileges, a collaborating VA clinician who is credentialed and privileged appropriately must be listed on the application. The collaborating clinician assumes responsibility for the specific procedures in question. This individual is then responsible for all study-related health care decisions and will be listed on the IRQ as the responsible clinician.
 - (c) Must submit the proposed research and obtain IRB approval or exemption from IRB review from the PVAMC IRB. As part of the review process, the Principal Investigator must comply with all requests for information to assess conflicts of interest.
 - (d) Initiate the study only **after** written approval by **both** the IRB and the R&D Committee is received. The R&D Committee has final responsibility of the scientific quality and appropriateness of all research involving human subjects.
 - (e) Adhere to all assurances given to the IRB at the time the project was approved.
 - (f) Forward the original signed informed consent form (VA Form 10-1086) for each patient enrolled in the research project to the R&D Service for scanning into the patient's electronic medical record. After the informed consent form is scanned into the patient's electronic medical record, the original signed consent form will be forwarded to the Principal Investigator for inclusion in the Principal Investigator's case history files. A copy must be given to the patient and the patient must initial the original signed consent form acknowledging receipt of a copy of the informed consent form.
 - (g) Create a progress note in the Computerized Patient Record System (CPRS) documenting the informed consent process with the patient, when the subject is actually entered into the study and when the human subject's participation is terminated.
 - (h) Submit all original adverse events occurring in the study to the IRB in a timely manner, consistent with the PVAMC policy.
 - (i) Complete annual review forms for continuing approval of ongoing research. The R&D Committee on an annual basis will assure the scientific quality of each active research protocol.
 - (j) Cite in the methods section of all manuscripts involving human studies at the PVAMC that the PVAMC IRB approved the project.

- (k) Fulfill all other responsibilities and adhere to the policies and procedures as outlined in the appropriate institutional, HRPP policies and procedures, and IRB SOP.

4. **Required Investigator Actions**

- (a) Specifically, the investigator is responsible for completing these reporting requirements to the IRB.

(1) Informed Consent:

The investigator must obtain informed consent from participants or the subject's legally authorized representative, prior to their enrollment into the research, using the informed consent document approved by the IRB, unless the IRB has approved a waiver of all of the requirements of informed consent or documentation of informed consent. Consent documents are valid until the "renew by" date stamped on the first page of the consent form and the investigator may use the forms only during the period for which they are valid. If an investigator would like to make any changes to the informed consent form, these changes must first be submitted to the IRB for review and approval. The investigator should submit a 1) Project Revision/Amendment Form detailing the changes to the informed consent form, 2) a clean copy of the modified informed consent form, and 3) a copy of the modified informed consent form with any changes highlighted. The process for obtaining informed consent will conform to regulations of the VA and FDA, the procedures described in this manual, and guidance issued by OHRP and ORD.

More information regarding informed consent may be found in Section VIII, IC, 800.

(2) Changes in Approved Research:

Changes in approved research, during the period for which approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to human subjects. Investigators must submit requests for changes, including proposed changes to consent forms to the IRB in writing. The proposed modifications should be submitted to the Research Service office with the "Project Revision/Amendment Form (PR/AF- Appendix C)."

Where changes are implemented to eliminate immediate hazards to subjects, the investigator must notify the IRB within 5 working days of making said changes. All other changes must be submitted to the IRB for review and approval, prior to implementation. If deviations from the approved protocol are discovered, they should be reported to the IRB as soon as possible. The investigator must also notify the IRB within 5 working days if FDA withdraws the approval of an approved IND or IDE or if a study is suspended or terminated by the sponsor.

More information regarding changes in IRB approved research may be found in Section VI, RR, 602, A.

(3) Continuing Review Approval:

Investigators are responsible for requesting reapproval in anticipation of the expiration of the approval period (generally 60 days before the expiration date). The investigator must submit the following for IRB continuing review approval: 1) continuing review questionnaire (CRQ); 2) any additional information as prompted and required by the CRQ; 3) Periodic Report of Human Subject Enrollment; 4) updated abstract; 5) clean

copy of proposed informed consent form; and 6) a copy of the modified informed consent form with any changes highlighted, if applicable.

More information regarding continuing review approval may be found in Section VI, RR, 602, D.

(4) Termination Reports:

Investigators are responsible for submitting study termination reports upon completion or termination of the study. The notice should be submitted on the "Research Project Termination Report" form. However, if at the time the continuing review paperwork is submitted to the IRB, the CRQ indicates that the study is terminated, then it is reviewed as a research project termination.

More information regarding termination reports may be found in Section VI, RR, 602, K.

(5) Adverse Event Reporting:

All investigators conducting research as employees or agents in the PVAMC are required to notify the IRB promptly of any serious adverse events (SAEs) or unanticipated problems involving risks to subjects or others that occur in research conducted at the PVAMC or by PVAMC employees or agents, or under VA auspices. Principal Investigators are also required to report promptly to the IRB any adverse event (AE) that is reported to ORO, the FDA and/or the sponsor in accordance with FDA requirements.

Principal Investigators should complete an Oregon Health & Science University (OHSU)/PVAMC Adverse Event Report Form for all adverse events occurring for studies approved by the IRB. The form is available online at: http://www.ohsu.edu/ra/irb/docs/sample_forms/aeform.doc. A copy of this form and the instructions are included in Appendix F. The form is one which tracks all adverse events which take place over the life of a protocol to allow tracking and enhanced monitoring of the adverse events.

More information regarding the reporting of adverse events is available in Section VI, RR, 602, G & H.

(6) Protocol Violations and/or Deviations:

Investigators must inform the IRB of any major and minor protocol deviations or violations. Violations/deviations can be any unplanned or unapproved research activity that is committed or omitted contrary to the terms of the IRB-approved research. Major deviations must be reported within 10 working days after the deviation becomes known. All other minor deviations, should be summarized to the IRB at the time of continuing review. Deviations from local HRPP, IRB, R&D Committee as well as state, VA and FDA regulations must also be reported to the IRB.

More information regarding protocol deviations may be found in Section VI, RR, 602, B.

(7) Long-Range Planning to Ensure Continuation of Research in the Event of the Absence of an Investigator:

This policy helps to ensure that when an investigator is called to active duty in times of war or national emergency, thus decreasing the number of staff available to conduct research, that the research will be conducted properly and more importantly, the proper treatment of the human subjects involved in the research will not be jeopardized.

If in the course of the research an investigator will be absent, the IRB must be notified regarding the investigator's change in activity on the research project. The Principal Investigator is responsible for notifying the IRB. The Principal Investigator or PVAMC Responsible Investigator must verify to the IRB that the quality of the research being conducted and the safety and treatment of the human subjects involved will not be compromised, i.e. whether or not treatment of the research subjects currently enrolled will continue and how these subjects will be monitored for safety per protocol.

If the Principal Investigator or PVAMC Responsible Investigator will be absent, active recruitment of research subjects into the research study must be suspended until the PI/PVAMC Responsible Investigator returns or until the Principal Investigator/PVAMC Responsible Investigator appoints a new individual to assume the absent investigator's responsibilities and justifies their credentials to perform the related responsibilities. The individual(s) must complete the required education and credentialing requirements, consistent with HRPP Policies & Procedures Nos. 4 and 10 as well as be credentialed and privileged to perform the absent investigator's responsibilities. The IRB must approve the individual(s) roles in the research project prior to the individual(s) beginning the work.

If a co-investigator will be absent, active recruitment in the research project does not need to be suspended, unless the individual's role in the research was essential and the individual will not be replaced while s/he is absent. If the co-investigator will be replaced, the individual(s) must complete the required education and credentialing requirements, consistent with HRPP Policies & Procedures Nos. 4 and 10 as well as be credentialed and privileged to perform the absent co-investigator's responsibilities.

If the Principal Investigator leaves the PVAMC, the original research records must be retained at the PVAMC.

G. PVAMC Subcommittees

The R&D Committee may require projects to be reviewed and approved by: the PVAMC Subcommittee of Research Safety (SRS), Institutional Animal Care and Use Committee (IACUC), and/or Subcommittee of Research Space; relevant committees of collaborating institutions and/or by ad hoc reviewers.

H. Regulatory Agencies

The IRB and IRB records are subject to regulation and inspection by governmental regulatory agencies (e.g. FDA, Office for Human Research Protections (OHRP), and the VA Office of Research Oversight (ORO). Copies of any applicable reports or correspondence to and from such agencies concerning the PVAMC R&D Committee must be provided by the IRB to the R&D Committee, which shall determine if any additional notifications are necessary.

I. IRB Staff and Resources

The IRB has full-time Coordinators, who report to the IRB Chairperson, the AO/R&D, and ACOS/R&D. The Coordinators act as a liaison between the investigators and the IRB. Space for the IRB Coordinators and IRB files is under the purview of the Research Service.

1. The IRB Coordinators are responsible for adhering to the responsibilities for the Research Service Administrative Staff as outlined in the MCM No. 151-01.
 - (a) Reviewing research proposal submissions, advising Principal Investigators about Federal, VACO, and local requirements for conducting research, placing research proposals on the appropriate subcommittee agenda, and coordinating the final approval by the R&D Committee.
 - (b) Maintaining IRB meeting calendars, minutes, membership information, membership education, study documentation and records in accordance with regulatory requirements.
 - (c) Tracking the progress of submitted research protocols.
 - (d) Fulfilling all other responsibilities and adhering to the policies and procedures as outlined in the appropriate institutional, HRPP, and R&D Service committee's policies and procedures.
2. Additionally, the IRB Coordinators are responsible for:
 - (a) Responding to requests for consultation, (i.e. questions regarding IRB policies and procedures, e.g. questions involving whether or not a project is considered human subjects research and whether it should be submitted to the IRB for review and approval) from investigators, research staff, clinicians, etc., received directly from the individual(s) or from the IRB Members and/or Chairs. This includes consulting with the IRB Members and Chairs if necessary to address an individual's questions.
 - (b) Scanning original informed consent forms into the patient's electronic medical record and ensuring that the original informed consent form is returned to the Principal Investigator.
 - (c) Assigning the primary and ad-hoc reviewers to review material submitted to the IRB. The IRB Chairs will assist the IRB Coordinators, as necessary, in completing this responsibility.
3. Contact information for the IRB Coordinators is included in Appendix I.

OM 301

IRB Membership and Responsibilities

(38CFR16.107; M-3, Part 1, Chapter 9.08; VHA Handbook 1200.5)

A. IRB Membership Requirements

The IRB membership is selected to assure: appropriate diversity, including consideration of race, gender, cultural backgrounds, and sensitivity to community issues and/or attitudes, as well as representation by multiple professions, knowledge and experience with vulnerable subjects and inclusion of both scientific and non-scientific members. The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects; and possess the professional competence necessary to review specific research activities.

NOTE: A member of the IRB may fill multiple membership position requirements for the IRB.

In addition to the diversity of membership based on consideration of race, gender and cultural background, each IRB will have at least:

1. Five members;
2. One member whose primary area of interest is scientific;
3. At least one member whose primary area of interest is non-scientific;
4. At least one member who is not affiliated with the Portland VA Medical Center or any of its components or other community based clinics such as Bend, Camp Rilea, Longview or Salem, and who is not part of the immediate family of a person who is affiliated with the medical center;

An **affiliated member** is one who works at the Portland VA Medical Center or any of its components or other community based clinics, such as Bend, Camp Rilea, Longview or Salem and/or is part of the immediate family of a person who is affiliated with the medical center. An individual who is a volunteer at the PVAMC is not considered an affiliated member.

5. Members of more than one profession;
6. One member from the Research & Development Committee; and
7. A Chairperson with a VA appointment.

B. IRB Roster

The current composition of the IRB in terms of members by name, degrees held, voting and alternate status and representative capacity is in Appendix D. In addition, the membership is summarized on the full board meeting minutes of the IRB.

C. IRB Chairperson

1. **Appointment**

One Chairperson for each IRB is nominated by the ACOS/R&D, voted on by the R&D Committee and formally appointed by the PVAMC Director. The Chair must hold a VA appointment, compensated or Without Compensation.

2. **Length of Service**

The Chairperson serves a one-year term and may be re-appointed indefinitely.

3. **Responsibilities**

- (a) Conducting IRB meetings;
- (b) Calling special meetings when necessary;

- (c) Consulting the IRB Coordinators to ensure operation of the IRB within all applicable regulatory requirements;
- (d) Reviewing and signing IRB minutes that summarize the actions and reasons for these actions of each presented item reviewed by the IRB;
- (e) Reviewing and acting on requests for exemption from IRB review, i.e., determining whether or not studies qualify for exemption from IRB review;
- (f) Reviewing requests for expedited review and, if the expedited process is appropriate, either approving the study on behalf of the IRB, or assigning a reviewer who will advise the Chair, so that the Chair can then act on the request on behalf of the IRB. Requests that do not meet the criteria for expedited review will be considered by a fully convened IRB.
- (g) Initially reviewing adverse event reports and determining whether or not immediate action is necessary in regards to patient safety;
- (h) The IRB Chairperson works with IRB members, institutional officials, and investigators to ensure that the rights and welfare of research subjects are adequately protected;
- (i) Signing the final IRB approval, VA Form 10-1223, unless the Alternate Chair is presiding, for protocols or actions approved by the IRB;
- (j) Notifying the RACC of any research-related complaints and allegations of non-compliance with HRPP institutional policies that have been raised by any individual. Reviewing research-related complaints and allegations of non-compliance with HRPP and IRB policies that have been brought forward from the RACC as well as determining whether a special meeting of the IRB must be convened if an immediate patient safety issue is raised or if the issue can be held until the next scheduled meeting.
- (k) Providing an initial orientation to IRB members to their committee activities and appropriate continuing education related to the IRB.
- (l) Forwarding any requests received for consultation received from investigators, research staff, clinicians, etc. to the IRB Coordinators for a documented response to the individual's questions. It is not the policy of the PVAMC IRB to provide curbside consults to individual investigators and medical staff.
- (m) Reporting to appropriate regulatory bodies consistent with VHA policies and procedures.
- (n) Fulfilling all responsibilities and adhering to the policies and procedures as outlined in the appropriate institutional, HRPP and R&D Service committee's policies and procedures.
- (o) Assisting the IRB Coordinators, as necessary, in assigning primary and ad-hoc reviewers to review material submitted to the IRB.

D. IRB Alternate Chairperson

1. Appointment

One Alternate Chairperson for each IRB is nominated by the ACOS/R&D, voted on by the R&D Committee and formally appointed by the PVAMC Director. The Alternate Chair must hold a VA appointment, compensated or Without Compensation.

2. Length of Service

The Alternate Chairperson serves a one-year term and may be re-appointed indefinitely.

3. Responsibilities

- (a) Performs responsibilities of the Chairperson in his/her absence.
- (b) Assists the Chairperson as needed.

E. IRB Members

(38CFR16.107)

1. Appointment

IRB members are nominated by the ACOS/R&D, voted on by the R&D Committee and formally appointed by the Medical Center Director.

2. Length of Service

Members serve 3-year terms and may be reappointed indefinitely. Regular attendance at IRB meetings is expected, and a member may be removed from the IRB on the basis of repeated unexcused absences or non-attention to the functions and responsibilities of the IRB. The R&D Committee reviews IRB membership annually.

3. Responsibilities

- (a) Members are responsible for ensuring that the rights and welfare of research subjects are protected.
- (b) Learning about, and remaining current on, ethical, legal and regulatory issues related to IRB business.
- (c) Completing the appropriate IRB reviewer forms.
- (d) Reviewing and assuring the Chair that all minor changes requested by the IRB were made for research projects contingently approved by the IRB.
- (e) Maintaining the integrity of the IRB review process. In particular, members must avoid discussing IRB protocols with investigators outside of a convened IRB meeting in a manner that would suggest possible IRB determinations.
- (f) Maintaining confidentiality regarding any information contained in any review.
- (g) Members vote to approve as presented, approve contingent upon the minor modifications have been made and verified by the Primary Reviewer(s) (contingent approval), table for major modifications, or disapprove research submitted to the IRB.
- (h) Members are expected to serve as primary reviewers when assigned, generally within their areas of expertise, and serve as general reviewers on all research discussed at convened meetings.
- (i) Members are expected to conduct expedited reviews on behalf of the IRB when so designated by the IRB Chairperson.
- (j) Members may be asked to participate in other subcommittees, audits, and education, as long as there is no conflict of interest with the IRB responsibilities.
- (k) In addition to completing the education requirements set forth by the IRB Chair, also successfully completing the education requirement in the protection of human research participants as indicated in HRPP Policy & Procedure No. 4.
- (l) As indicated in HRPP Policy & Procedure No. 5, avoiding conflicts of interest or the appearance of conflicts of interest. The IRB Chairpersons and members may find themselves in any of the following potential conflicts of interest when reviewing research:
 - (1) Where an IRB Chairperson or member is listed as an investigator on the research.
 - (2) Where any investigator must report to or is under the supervision of an IRB Chairperson or member.
 - (3) Where an IRB Chairperson or member competes for research grants or contracts in the same or similar field as an investigator whose research is scheduled for review.
 - (4) Where an IRB member is a family member of an investigator whose research is scheduled for review.

- (m) For further information regarding the responsibilities of an IRB member and conflict of interest in human research, please see the Human Research Protection Program: Policy & Procedure No. 5, "Conflict of Interest in Human Research," located in Appendix M.
- (n) Forwarding any requests for consultation from investigators, research staff and clinicians, etc. received to the IRB Coordinators for a documented response to the individual's questions. It is not the policy of the PVAMC IRB to provide curbside consults to individual investigators and medical staff.
- (o) Fulfilling all responsibilities and adhering to the policies and procedures as outlined in the appropriate institutional, HRPP and R&D Service committee's policies and procedures.

F. Alternate IRB Members

1. Appointment

Alternate members may be nominated by the ACOS/R&D, voted on by the R&D Committee and appointed by the Medical Center Director. These alternates are nominated with the same criteria of selection as IRB members.

2. Length of Service

An alternate IRB member's length of service may be based upon one of the following:

- (a) the individual's term as an IRB member, if already a full time IRB member;
- (b) the term of the individual s/he is representing; or
- (c) a three-year term, if the individual serves as an alternate for multiple full time IRB members.

3. Responsibilities

An alternate IRB member has the same responsibilities as a full time IRB member listed in Section III, OM, 301.E.

These alternates replace regular IRB members who are, on occasion, unable to attend convened meetings of the IRB. All alternates are identified on the IRB Alternate rosters in Appendix D and are identified as to whom they may substitute at convened meetings. IRB minutes will record when alternate members act in the absence of primary members. All alternate members will receive the same reviewer information as primary IRB members when they will be attending meetings for the absent member. The alternate member is allowed to vote in the absence of the member s/he represents.

G. Ex-Officio Members

The IRB does not include "non-voting" members, other than ex-officio members, who are appointed due to their position at the PVAMC. These members must adhere to the same conflict of interest policies and procedures as the voting IRB members. The ex-officio members may not vote with the IRB. These members are not nominated and appointed by the Medical Center Director. The Administrative Officer/Research & Development serves as an ex-officio member of the IRB.

H. Individuals with Special Expertise (Ad Hoc Members/Use of Consultants)

(M-3, Part 1, Chapter 9.08(f), VHA Handbook 1200.5 6.h., 38 CFR 16.107(f))

On an as-needed basis, the IRB may, at its discretion, invite individuals with competence in special areas to assist in the review of any issues which require expertise beyond or in addition to that available on the IRB. This may include the review of a study involving a clinical procedure or specialty not represented on the IRB. The IRB members and/or Chair may determine that the IRB needs additional technical assistance.

Recommendations for consultants may come from the ACOS/R&D, R&D Committee members, IRB members, and/or medical staff. The ad hoc reviewer will be invited to review the research project and will be provided documented expectations and a charge. The IRB Chair and/or Coordinators will make the arrangements for such a review. The ad hoc reviewer must adhere to the same conflict of interest policies and procedures as the IRB members. The ad hoc reviewers may attend the IRB meeting when the study is reviewed, however, their presence or absence will not be used in establishing a quorum for an IRB meeting. The ad hoc reviewers may not serve as the primary reviewer, nor may they vote with the IRB. An ad hoc reviewer may provide guidance and expertise either in person or through written comment. The qualifications and comments of the ad hoc reviewer will become part of the documentation supporting the IRB deliberations.

I. Compensation for IRB Service

IRB members are not compensated for serving on the IRB, but may receive reimbursement for travel costs.

OM 302**Training of IRB Chairs and Members**

As a condition of the FWA, IRB members are provided education about human research protection.

A. Responsibilities

The IRB Chairs and Members are responsible for meeting the educational requirements as set forth in the PVAMC Human Research Protection Program: Policy & Procedure No. 4, "Education for the Protection of Human Research Participants in the Research & Development Service," and for any other education as required by the IRB Chair. The HRPP: Policy & Procedure No. 4 is located in Appendix L.

It is the responsibility of the Chairperson of the IRB #1, and the Research Service to provide members with an initial orientation to their committee activities and appropriate continuing education related to the IRB.

B. IRB Standard Operating Procedures

All IRB members receive a copy of the PVAMC IRB SOP Manual prior to their first meeting with the IRB.

This IRB SOP Manual includes the IRB SOP and its appendices, in addition to a complete section of pertinent regulations.

C. Continuing IRB Education

The IRB members are responsible for completing the annual educational requirements as set forth in the PVAMC Human Research Protection Program: Policy & Procedure No. 4, "Education for the Protection of Human Research Participants in the Research & Development Service."

In addition, the IRB Chair and/or RACC present educational sessions that may occur quarterly at the IRB meeting.

D. New IRB Member Training

Each new IRB member's training, as of January 2004, consists of the following:

1. Members are given a copy the IRB SOP Manual which contains all relevant educational materials.
2. The IRB Chair discusses with the member(s) the parameters of IRB decision-making and answers any questions the new IRB member(s) may have regarding his/her/their responsibilities as an IRB member(s) and the functioning of the IRB.
3. The IRB Chair also presents an educational course where he discusses the development of the IRB within the United States and focuses on contemporary issues facing the PVAMC IRB in its review of protocols in light of contemporary issues in research related to study participants.
4. The IRB Chair presents contemporary topics facing IRBs in the United States in a didactic question and answer session that can occur quarterly at the IRB meeting.
5. Each new member is assigned studies to review based on the unique expertise of the member, i.e. strengths, education, and experience levels.
6. A description of the responsibilities of an IRB member.

7. An overview of the administrative aspects of the committee functions.

EI 401**Exemption from IRB Oversight/Review
(38 CFR 16.101(b)(1-6))**

Investigators shall submit a written request to the IRB for an exemption from IRB review. This should be completed through the "Certification of Exemption Form." The IRB serves as the R&D Committee's designee in the review of exempt status based on categories stipulated at 38 CFR 16.101.

The IRB Chair or the Chair's qualified designee, will recommend approval of the exempt status to the R&D Committee. Documentation regarding the rationale for the exemption, the category and circumstances will be completed by the IRB Chair or the Chair's qualified designee and will be maintained in Research Service records. The decision of exempt status must be communicated in writing to the investigator and the IRB. The IRB will be notified of the review and decision at the next convened IRB meeting and it will be documented in the meeting minutes.

A project that is exempt from IRB review must be reviewed by the R&D Committee, prior to initiation. The R&D Committee will review the project and make a final determination (M-3, Part1, Chapter 9.06). The research project may begin once written confirmation from the IRB and R&D Committee has been received. Once approved by the R&D Committee, the project must be included in the R&D Committee's annual review of research projects.

Any individual involved in making the determination of exempt status of a proposed research project cannot be involved in the proposed research.

Categories of exempt research are stipulated in VA regulations at 38 CFR 16.101(b)(1-6) and the Common Rule as follows:

- (1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as: (a) research on regular and special education instructional strategies, or (b) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
- (2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (a) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (b) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
- (3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2)(b) of this section, if: (a) The human subjects are elected or appointed public officials or candidates for public office; or (b) federal statute(s) require(s) without exception that the

confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

- (4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
- (5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (a) Public benefit or service programs; (b) procedures for obtaining benefits or services under those programs; (c) possible changes in or alternatives to those programs or procedures; or (d) possible changes in methods or levels of payment for benefits or services under those programs.
- (6) Taste and food quality evaluation and consumer acceptance studies, (a) if wholesome foods without additives are consumed or (b) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration (FDA) or approved by the Environmental Protection Agency (EPA) or the Food Safety and Inspection Service of the U.S. Department of Agriculture. This also applies to FDA regulated research.

Note: These exemptions are not available for all kinds of research (38 CFR 16.101(i)). There are restrictions based on the populations to be studied: research involving prisoners or focused primarily on pregnant women, human in vitro fertilization or fetuses may be exempted, and research that falls in category (2) may not be exempted when children are subjects if the investigator will interact with the child, as in survey or interview research.

FO 501

IRB Recordkeeping and Required Documentation (38CFR16.115)

A. Record Retention

(38 CFR 16.115(b), 45 CFR 164.528)

The IRB shall keep records for at least six years after consideration for disapproved proposals and six years after the conclusion of research for approved proposals or as required by study sponsors, as indicated through the IRQ. All IRB records collected over the course of the protocol will be maintained by the IRB Coordinators in the PVAMC Research Service space. If a study does not receive funding and the PI decides not to conduct the research without funding, the records will also be kept for six years. If an investigator leaves the PVAMC facility, the original research records must be retained at the PVAMC for six years.

B. Access to IRB Records

(38 CFR 16.115(b))

IRB records are the property and the responsibility of the PVAMC Research Service office. These records are stored by the Research Service at the PVAMC either in the Research Service office, or in storage areas in locked file cabinets behind magnetic security doors in order to maintain the privacy and confidentiality of research subjects' information. Electronic records are kept on a password-protected computer maintained by the Research Service staff as part of their official employment duties.

IRB records are accessible to the Research Service staff, IRB Chair and members, as well as the R&D Committee Chair and members for committee purposes only. Research investigators shall be provided reasonable access to files related to their research. Other authorized individuals, such as accrediting officials and officials of Federal and state regulatory agencies, including the: Office of Research Oversight (ORO), the Office for Human Research Protections (OHRP), and the Food and Drug Administration (FDA), will have access to IRB records for inspection and copying upon determination of appropriateness and necessity at reasonable times and in a reasonable manner. Appropriate accreditation bodies shall be provided access and may recommend additional procedures for maintaining security of IRB records.

A log of individuals who do access the IRB records, excluding the IRB members whom review the IRB records for committee purposes only and Research Service staff, is maintained by the IRB Coordinators and/or Research Service staff.

C. IRB Records

The IRB records include:

1. Standard Operating Procedure Manual
2. Documentation of convened IRB meeting minutes
3. IRB Membership Information
4. Education/Training Records
5. Research project files

Research project records are in organized files and contain all documentation associated with the research project. This includes the research proposal reviewed, records of continuing

review activities, copies of all correspondence between the IRB and the investigator, as well as scientific evaluations, sample consent documents, progress reports and any reports of injuries to subjects, when applicable.

6. Federalwide Assurance (FWA)

D. IRB Membership Roster

The IRB Coordinators maintain the current IRB membership rosters and periodically report any changes to the OHRP with a copy to the Office of Research Oversight (ORO). The IRB Coordinators are responsible for maintaining updated IRB rosters. The rosters include name, degrees held, voting and alternate status and representative capacity (i.e., pharmacy, non-scientific member, etc.). The IRB membership rosters are included in Appendix D. The IRB Membership Information binder contains copies of the IRB members' Curriculum Vitae or equivalent and appointment letters.

E. Education Records

The Research Service office shall maintain accurate records of research investigators, research staff, IRB members, and IRB staff who have fulfilled the PVAMC HRPP education requirements.

Please see the Human Research Protection Program: Policy and Procedure No. 4, Education for the Protection of Human Research Participants in the Research & Development Service, for a detailed description of the education requirements and the individuals required to complete the requirements. The Research Assurance & Compliance Coordinator is responsible for maintaining and monitoring the tracking database for all individuals completing the HRPP education requirements as described in this policy.

The IRB Coordinators are responsible for maintaining any additional education and training records of IRB members.

F. Written Standard Operating Procedures

(38 CFR 16.103(b) (4, 5) and 108(a), 115(a)(6))

IRB members are provided with a copy of the PVAMC IRB SOP both electronically and hard copy at the time they join the IRB, and each time the SOP is updated.

The ACOS/R&D, AO/R&D, IRB Chairpersons, IRB Coordinators, and Research Assurance & Compliance Coordinator work together to write and maintain the IRB SOP. The SOP will be reviewed and modified as needed to reflect updated and applicable regulations, policies, and institutional procedures.

G. IRB Correspondence

(38 CFR 16.115(a)(4))

Accurate records are maintained of all communications to and from the IRB. IRB correspondence is signed by an IRB Coordinator present at the meeting or at such time as the text of such correspondence is confirmed with the IRB Chair. Copies of all correspondence are filed in the appropriate investigator research project file, which are located in the PVAMC Research Service office or designated storage area.

Upon initial review, results of that review are sent to the principal investigator or designated study coordinator within three weeks of the convened meeting date. In cases of contingent approval, the results of the review of submitted items are sent to the principal investigator or designated study

coordinator within a reasonable time frame upon the resolution of items reviewed outside of a convened meeting.

In cases in which a project being performed at the PVAMC has multiple investigators, correspondence will be sent to the investigator primarily in charge of the study or to the study coordinator designated to receive such correspondence, as noted on the IRQ or PPQ. If the study coordinator is designated to receive such correspondence as noted on the IRQ or PPQ, the study coordinator will be responsible for communicating the results of the review to the principal investigators. The principal investigator is ultimately responsible for the research project and assuring that the research project and staff comply with IRB requirements. In cases where communication is electronic, upon resolution of the topic of the communication, a hard copy will be generated and filed with the project file by the IRB Coordinator and/or staff.

H. IRB Research Project Files

The IRB shall maintain a separate file for each research project. Protocols are assigned a unique number from the Manage Your Institutional Review Board (MIRB) Database for tracking and administration purposes. A separate unique VA grant number is also assigned, and is associated with each protocol. This VA grant number serves as another method of identifying the grant. The IRB application shall include the IRB forms, as applicable to the protocol.

I. Research Tracking System

The IRB uses a reliable computerized tracking system, the MIRB computer program, which is maintained by the IRB Coordinators and Research Service staff. MIRB stores information regarding which documents have been received, when they were reviewed, and the results of that review.

Additionally, MIRB tracks changes that are needed, when those changes were received and approved, and the date of continuing review for research projects reviewed by the IRB.

MIRB is used to track IRB membership, as well as generate IRB agendas, correspondence and minutes.

J. Activities Requiring IRB Review

Projects meeting the definition of research and involving human subjects and/or human data and/or human biological specimens, conducted at the PVAMC, must undergo IRB and R&D Committee review and approval before the research project may begin. The IRB and R&D Committee will determine whether or not the research activity is exempt from the human subjects regulations and purview of the IRB. Questions regarding whether or not IRB review and approval is required, must be directed in writing to the IRB Coordinators. Requests for determination submitted to the IRB Coordinators should include a detailed explanation of the research question and how the research will be conducted. The IRB Coordinators will forward written requests to the IRB when necessary.

K. Documentation of Exemptions from IRB Oversight/Review

The IRB Chair or the Chair's qualified designee, generally the IRB Alternate Chair, will recommend approval of the exempt status to the R&D Committee. Documentation regarding the rationale for the exemption, the category and circumstances will be completed by the IRB Chair or qualified designee and will be maintained in Research Service records. The decision of exempt status must be communicated in writing to the investigator and the IRB. The IRB will be notified of the review and decision at the next convened IRB meeting and it will be documented in the meeting minutes.

More information, regarding the determination of Exemption from IRB Oversight/Review is located in Section IV, EI, 401.

L. Documentation of Expedited Reviews

(38 CFR 16.110(b); 63FR 60364-60367, November 9, 1998)

Upon request by a principal investigator for expedited review, the Chair or the Chair's qualified designee will review the material to assess the appropriateness of the request. In cases where an expedited review is appropriate, the Chairperson or qualified designed if the Chair is not available will conduct such review. The review will be documented in the research project file and the next meeting minutes of the IRB. Expedited review will only be used in cases which meet all expedited review requirements, referenced in Section VII, EX,700.

M. Documentation of Convened IRB Meetings – Minutes

(38 CFR 16.115(a)(2))

IRB minutes are completed by the IRB Coordinators in MIRB. Minutes shall include:

1. Attendance by name at the meeting;
2. Call to order, which documents that the required quorum was present for each vote, including a non-scientific member;
3. Approval of prior meeting minutes;
4. New and Old Business;
5. Actions taken by the IRB on the following: initial or continuing review of research, specific measures taken to protect vulnerable populations, review of protocol or informed consent modifications or amendments, unanticipated problems involving risks to subjects or others, adverse event reports, reports from sponsors, cooperative groups, or Data Safety Monitoring Boards (DSMB), reports of continuing non-compliance with the regulations by investigators and other staff or IRB determinations, waiver or alteration of elements of informed consent and justification, suspensions or terminations of research, and other actions as appropriate;
6. Votes on each action reviewed by the IRB, including the number of members voting. These are categorized according to the following: “for, against, abstained, recused, and excused.”
Abstained is used when a member states that s/he would like to refrain from the vote voluntarily. For example, a member may refrain from a vote if s/he was only present for a portion of the discussion of a particular item.
Recused is used when a conflict of interest has been identified for a member of the IRB. The member is excused from the room and not allowed to participate in the deliberations or vote on the research project.
Excused is used when a member of the IRB was out of the room for the vote, i.e. restroom, emergency, etc.
7. The basis for requiring changes in or disapproving research;
8. Summary of controverted issues and their resolutions. An issue is controverted when there is a split vote, in which some IRB members vote for approval and other IRB members vote against approval. When a split vote is recorded, the summary of the controverted issue must be documented.;
9. A list of research approved since the last meeting utilizing expedited review procedures and the specific citation for the category of expedited review of the individual protocol;

10. Approvals of minor changes, utilizing expedited review procedures, in previously approved research during the period for which approval is authorized and the specific citation for the category of expedited review of the minor changes;
11. Stipulations met and final approval letters issued for items contingently approved at a convened IRB meeting, once those changes have been submitted by the investigator, verified by the designated IRB primary reviewer and approved by the IRB Chair;
12. The names of persons who excused themselves during the review of a protocol; and
13. Determination of the frequency of continuing review of each research project based upon the degree of risk, as determined by the IRB.

Once approved by the members at a subsequent IRB meeting, the minutes must not be altered by anyone including a higher authority. After being signed by the IRB Chair, a copy of the IRB meeting minutes will be forwarded to the R&D Coordinator and available for R&D Committee review within three weeks of the convened meeting. These minutes may be reviewed by the R&D Committee at the next convened R&D Committee meeting.

N. **Attendance at IRB Meetings**

IRB minutes shall list attendance according to the following:

1. Names of members present, according to their voting status;
2. Names of absent/excused members, according to their voting status;
Excused is used when a member has notified an IRB Coordinator in advance of the meeting that s/he will be absent.
Absent is used when a member has not notified an IRB Coordinator in advance of the meeting that s/he will be absent.
3. Names of alternates attending in lieu of specified (named) excused/absent members.
Alternates may substitute for specific excused/absent members only as designated on the official IRB membership roster;
4. Names of ad hoc reviewers present;
5. Names of Research Service Staff present and/or excused/absent; and
6. Names of guests present.

Note: (2) – (6) will be documented as appropriate.

O. **Quorum Requirements and Voting at IRB Meetings**

(M-3, Part 1, Chapter 9.09.e, VHA Handbook 1200.5 7.f.)

The IRB will not conduct business without a quorum present, which must include the presence of a non-scientific member. A quorum is always maintained and a non-scientific member is always present during a convened meeting, unless otherwise stated in the meeting minutes. The IRB follows the following rules, regarding quorum requirements, during the IRB meeting.

1. A majority of the IRB members (or their designated alternates), including at least one member whose primary concerns are in nonscientific areas, must be present to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting.
2. Members may be present in person or audio (telephone) or audio-visual teleconference. Members present via teleconference shall be noted as such in the meeting minutes, which

shall also indicate that the members received all pertinent information prior to the meeting and were able to actively and equally participate in all discussions.

3. IRB minutes shall include documentation of quorum and votes for each IRB action and determination by recording votes number voting: for (); against (); abstained (); recused (); excused ().
4. Members absenting themselves due to conflicts of interest will be documented as “recused” during the vote. The member may not be counted toward quorum requirements (i.e., may not be counted among those voting for, against or abstained) or be counted as among the majority of members necessary to constitute a quorum.
5. The following individuals will not be considered as part of the quorum and will not vote with the IRB:
 - (a) An individual who is not listed on the official IRB membership roster;
 - (b) Any ex-officio member of the IRB;
 - (c) Ad Hoc reviewers;
 - (d) Consultants;
 - (e) Guests; and
 - (f) Research Service Staff.
6. At least one non-scientist must always be present for a vote to be taken. If a non-scientific member of the IRB is absent during the meeting, i.e. if the non-scientific member is absent or excused, this is indicated in the meeting minutes.
7. When a member and his/her alternate both attend a meeting, only one can vote.
8. If research involving an FDA regulated device is to be reviewed, a licensed physician must be included in the quorum.

P. Actions Taken by the Convened IRB

(38 CFR 16.109; 115)

The minutes shall include all actions taken by the convened IRB and the votes underlying those actions.

IRB actions for review of research include the following:

1. **Approved (Approved with no changes or no additional changes).** If it is the **initial** review of the research project, IRB, R&D Committee and any other applicable subcommittee written approvals are required **prior** to study initiation.
2. **Contingent Approved (Approved with minor changes)** to be reviewed by a designated IRB member. Such minor changes must be clearly delineated by the IRB so the investigator may simply comply with the IRB’s stipulations. The research may proceed after the required changes are verified by the designated reviewer and approved by the IRB Chair and the investigator has received final written approval from the IRB, R&D Committee and any applicable subcommittees. Note: A study undergoing initial review that has been contingently approved by the IRB may proceed to be reviewed by the R&D Committee. The study may not begin until final approval by both committees and any other applicable subcommittees are received.
3. **Tabled** pending receipt of additional substantive information or substantive changes. The IRB determines that it lacks sufficient information about the research to proceed with its review or that the changes are so numerous as to require re-review by the full board. This category is referred to as “Tabled” in the IRB correspondence and minutes. The research

may not proceed until the convened IRB has approved a revised application at a convened meeting and the investigator has received final written approval from the IRB, R&D Committee and any applicable subcommittees.

4. **Disapproved.** The IRB has determined that the research cannot be conducted at the facility or by employees or agents of the facility.

IRB actions, during the review of adverse events occurring during the period for which the research project is authorized and also at the time of continuing review, determine whether or not the **risks to subjects** have changed and decide whether or not the research:

1. May continue as presented, i.e. approved action;
2. May continue with modifications, i.e. contingent approved or tabled action. If the continuing review of a research project is tabled because of substantive modifications, it must be re-reviewed and approved by the IRB, prior to the expiration date to avoid a lapse in IRB approval;
3. Must be suspended, i.e., disapproved action; or
4. Must be terminated, i.e., disapproved action.

Q. Situations of IRB Deferral

A deferral may be documented in the IRB minutes when the IRB did not take an action on an item scheduled for review because a quorum would be lost or if the IRB primary reviewer(s) were not present at the meeting to present the item s/he reviewed. The review of the item will be postponed until the next scheduled meeting, as appropriate.

R. The Basis for Requiring Changes in or Disapproving Research **(38 CFR 16.109(d))**

The minutes of IRB meetings shall include the basis for requiring changes in or disapproving research.

Principal Investigators or their designated coordinators as indicated on the IRQ or PPQ shall be notified in writing of the determination of the IRB, and any changes that are required by the IRB. These will be sent electronically via e-mail, and a signed hard copy of the correspondence will be mailed to the designated individual for the Principal Investigator's research project files. Responses to the IRB should come from the investigator or designated study coordinator, and may be communicated electronically or by hard copy.

Prior to final approval, the changes the IRB has requested must be reviewed and confirmed by either the designated IRB primary reviewer or the convened IRB, whichever the IRB has designated. If an item has been tabled, the appropriateness of the changes must be re-reviewed by the convened IRB. If an item has received contingent approval the appropriateness of the changes need to only be reviewed by the IRB primary reviewers.

Upon final review and approval by the IRB, VA Form 10-1223, appropriate with Section V, FO, 501, S below, will be completed and signed by the IRB Chairperson.

S. Use of VA form 10-1223, Report of Institutional Review Board

The respective IRB chair signs VA form 10-1223 when the IRB approves new protocols, changes to protocols, or revised informed consent forms. Specifically, form 10-1223 is generated for signature of the IRB chair in the following circumstances: at the time of initial approval, at the time of continuing

review approval, any time a protocol amendment or revised consent form is reviewed and approved, at the time a revised investigator's brochure is reviewed and approved, and at the time of approval of any change to the protocol or research team which affects the manner in which the research is conducted, such as addition to the research team or a change of age range of potential participants.

VA form 10-1223 is not generated in cases where the IRB review is for the purposes of assuring ongoing patient safety, but a change in the research conduct is not indicated. This includes review of adverse events, review of reports of protocol deviations, and review of notifications, which are informational only. The IRB reserves the right to request more information or a change in the research procedures, however, in cases of initial review of adverse events and reports of informational nature, it is inappropriate to generate VA form 10-1223. In these cases, the IRB coordinators will generate a separate memorandum noting whether or not any further action is needed on the part of the principal investigator or research coordinator.

T. Summary of Controverted Issues at Convened Meetings

(38 CFR 16.115(a)(2))

The minutes of IRB meetings shall include a written summary of the discussion of controverted issues and their resolution. An issue is controverted when there is a split vote, in which some IRB members vote for approval and other IRB members vote against approval. When a split vote is recorded, the summary of the controverted issue must be documented.

U. IRB Findings and Determinations where Documentation is Required by Regulation

(OHRP and FDA Guidance)

The IRB members shall use the appropriate "IRB Primary Reviewer Form" in reviewing protocols at the time of initial and continuing review. A copy of the checklists is included in Appendix E. IRB determinations, regarding the following items are documented in the IRB minutes and/or correspondence.

1. The level of risk of the research.
2. The approval period for the research, including identification of research that warrants review more often than (at least) annually.
3. Justification for waiver or alteration of informed consent and/or HIPAA Authorization, addressing each of the four (4) criteria at 38 CFR 16.116(d). (Note: This cannot be done if an FDA test article is involved.)
4. Justification for waiver of the requirement for written documentation of informed consent in accordance with the criteria at 38 CFR 16.117(c).
5. For DHHS-supported research, justification for approval of research involving pregnant women, human fetuses, and human in vitro fertilization, addressing each of the criteria specified under 45 CFR 46 Subpart B of the DHHS human subject regulations. **Note:** The PVAMC does not review or conduct research directly involving human fetuses or human in vitro fertilization.
6. For DHHS-supported research, justification for approval of research involving prisoners, addressing each of the categories and criteria specified under 45 CFR 46 Subpart C of the DHHS human subject regulations. Generally, the IRB Coordinator is responsible for providing certification of the IRB's findings to OHRP. **Note:** The PVAMC does not review or conduct research with prisoners.
7. For DHHS and VA supported and FDA regulated research, justification for approval of research involving children, addressing each of the categories and criteria specified under 45

CFR 46 Subpart D of the DHHS and FDA human subject regulations. VA policy specifies that a waiver for research involving children must be obtained from the Chief Research and Development Officer, Office of Research & Development (VHA Directive 2001-028, April 27, 2001). Generally the IRB Coordinator is responsible for providing notification to OHRP of the IRB's findings concerning research requiring review by a panel of experts convened in accordance with Subpart D. For FDA regulated research documentation of the IRB findings is required. Notification shall go to the Commissioner of the FDA. **Note:** The PVAMC does not review or conduct research with minors.

8. The IRB's consideration of the additional safeguards to protect the rights and welfare of vulnerable subjects. For example, the special protections warranted in specific research projects for groups of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, regardless of source of support for the research.
9. Justification for approval of research planned for an emergency setting, with specific reference to the criteria specified under the special 45 CFR 46.101(i) DHHS waiver or the FDA exception at 21 CFR 50.24. (Note: VA researchers cannot use these provisions. Please refer to Policy Clarification and e-mail dated 10/04/2002, regarding No Planned Emergency Research in Appendix U.)

FO 502**IRB Meetings
(Review by the Convened IRB)
(38 CFR 16.108(b))**

The IRB will conduct initial and continuing reviews of all non-exempt research at convened meetings at which a quorum of the members is present, including a member whose primary interest is non-scientific, unless the research falls into one or more categories appropriate for expedited review.

A. IRB Meeting Schedule

The current IRB meeting schedules are listed in Appendix D as well as in the Research Service office. Principal Investigators must submit information to the Research Service office by the 20th of the month for review at one of the following month's scheduled IRB meeting. The IRB agenda, minutes, review materials and all applicable primary reviewer materials are dispersed to the IRB members approximately one week prior to the next convened meeting to allow for sufficient review in order to discuss the items for review adequately and determine the appropriate action during the convened meeting. IRB review materials include all of the materials as described in Section FO 504. Once a research project is reviewed by either IRB #1 or #2, the research project will stay with the same IRB for the life of the protocol.

Unless otherwise noted, the PVAMC IRBs will meet in Bldg. 101, Room 433.

B. Agenda

A meeting agenda will be prepared by the IRB Coordinators or designee and distributed with the meeting materials to IRB members prior to each meeting.

C. IRB Meeting Procedures

The IRB Chair or Alternate Chair if the Chair is not present will call the meeting to order, once a quorum is established. The IRB will review and discuss the IRB minutes from the previous meeting and determine whether or not any changes to the minutes are necessary. If no changes are requested, the minutes will be considered final as presented.

The IRB will review and discuss each item to be reviewed by the IRB on the agenda and either take action on each item or defer the item as appropriate.

The IRB Coordinators are responsible for taking minutes at each IRB meeting.

D. Use of Subcommittees to Support IRB Activities

The IRB Chairperson may appoint subcommittees on an ad hoc basis to perform non-review functions as needed, such as monitoring compliance with IRB regulations.

FO 503**Use of Primary Reviewers with Convened IRB Reviews****A. Assignment of Primary Reviewers**

The IRB Coordinators of the Research Service will make a preliminary review of the IRB application at the time of receipt and generally assign at least two primary reviewers at the time of initial and continuing review to review the protocol for the next IRB meeting, according to consistency with the protocol content and reviewer knowledge and expertise. The IRB Chairs will assist the IRB Coordinators, as necessary, in completing this responsibility. Physicians, Pharmacist, Nurses, PhD, and Masters level physical, biological, or social scientists, as well as other biomedical health professionals are considered to have primary concerns in the scientific area. In general, two reviewers will be assigned, but for more complex research project proposals, additional reviewers may be assigned.

All other events reviewed by the IRB, with the exception of the initial and continuing reviews, will be assigned one primary reviewer consistent with the protocol content and reviewer knowledge and expertise.

B. Responsibilities of Primary Reviewers

The primary reviewers for each item reviewed by the IRB, including the initial review, and for continuing review, are considered the lead reviewers on the IRB for the research project assigned to them. They are responsible for:

1. being thoroughly versed in all details of the research;
2. conducting an in-depth review of the research;
3. completing the applicable IRB reviewer forms contained in Appendix E; and
4. leading the discussion of the research at the convened meeting, voicing any concerns that arose during their review and changes that may be required.

C. Absentee Primary Reviewer

If a reviewer is absent from the meeting a new reviewer may be assigned, as long as the new reviewer has reviewed the requisite materials prior to the meeting. An absent reviewer can submit their written comments to be read at the meeting, as long as another reviewer is present to serve as a primary reviewer.

FO 504**Materials for IRB Review**

All IRB members, including alternate members and consultants, when applicable, shall be provided with sufficient information to ensure thorough initial and continuing review of each research proposal. The IRB members will receive these materials approximately one week prior to the scheduled convened meeting. All IRB members shall be afforded full opportunity to discuss each research proposal during the convened meeting.

A. Initial Review Materials

1. **All IRB members** will receive a copy of the below materials, during the initial review of a research project:

| Item for Review | Additional Information |
|---|---|
| Initial Review Questionnaire and any additional attachments | Attachments include the Human Biological Specimens Questionnaire, Investigational Device or Drug Information Record, or Conflict of Interest in Human Research Form, etc. |
| Abstract, i.e. protocol summary | NA |
| Informed consent form or Request for Waiver of Informed Consent Requirements and Authorization to Release Medical Records or Health Information, if applicable | NA |
| HIPAA Forms, if applicable | NA |
| Advertisements or other materials provided to subjects, if applicable | NA |

2. **The Primary IRB Reviewers** for each research projects will receive the above stated materials in addition to the following for each research project. **Note:** during the initial review of a research project, the entire IRB file is given to the primary IRB reviewers prior to the convened meeting.

| Item for Review | Additional Information |
|-----------------|---|
| Protocol | The protocol must include a written plan for a research study that includes, at a minimum, a description of the objectives, rationale, design and methods to be used in |

| | |
|--|--|
| | the conduct of the research. |
| Investigator's brochure(s) or equivalent material, if applicable | This is required if the study involves an investigational drug. If the investigator is the sponsor of the study, an Investigator's Brochure or equivalent material is required. If a study involves a FDA-approved drug, an Investigator's Brochure may not exist. For such a study, equivalent information should be provided (package insert). |
| Subject Surveys, questionnaires, if applicable | NA |
| Merit Reviews or Grant Applications, if applicable | NA |
| Any other applicable material submitted by the Principal Investigator in order to have the complete application to ensure a thorough initial review of the research project proposal. This may include phone scripts. | NA |

B. Continuing Review Materials

1. **All IRB members** will receive a copy of the below materials, during the continuing review of a research project:

| Item for Review | Additional Information |
|--|--|
| Continuing Review Questionnaire (CRQ) | The CRQ identifies whether or not: any additional adverse events have occurred that have not been reported to the IRB; new information is available regarding the research project that may change the risk/benefit ratio; any research finds to date, including summary of subject experiences (benefits, adverse reactions); any unanticipated problems involving risks to subjects; and enumeration of subjects withdrawn and the reasons for withdrawal. |
| Updated Research Project abstract, i.e. protocol summary | NA |
| Most current IRB approved informed consent form. | NA |

2. **The Primary IRB Reviewers** for each continuing review of a research project will receive the above stated materials in addition to the following for each research project to help ensure a thorough continuing review of the research project. **Note:** During the continuing review of a research project, upon request, any IRB member also has access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting.

| Item for Review | Additional Information |
|---|--|
| Continuing Review Questionnaire (CRQ) | The CRQ identifies whether or not: any additional adverse events have occurred that have not been reported to the IRB; new information is available regarding the research project that may change the risk/benefit ratio; any research finds to date, including summary of subject experiences (benefits, adverse reactions); any unanticipated problems involving risks to subjects; and enumeration of subjects withdrawn and the reasons for withdrawal. |
| Updated Research Project abstract, i.e. protocol summary | NA |
| Most current IRB approved informed consent form | NA |
| Complete protocol | NA |
| Most recent Serious Adverse Event log capturing all SAEs to date, if applicable | If the research involves no risk and is non-interventional or if no subjects have been enrolled, this factor is not applicable. If the research is not FDA-regulated, sponsor safety reports are not required. |
| Amended or updated Investigator's brochure, if applicable | If the research project does not involve a drug or device, this is not applicable. |
| Summary of safety monitoring reports, if applicable | If the protocol is minimal risk, and it does not include a data monitoring plan, this is not applicable. |

FO 505

Notifications of IRB Review (38 CFR 16.109(d) and 115)

A. Notification to the R&D Committee

The IRB shall notify the R&D Committee in writing of its determinations as determined in Section V, FO, 501. The R&D Committee is notified of all IRB determinations of items for review through the review of the IRB meeting minutes.

It is the responsibility of the IRB Chairs and/or the ACOS/R&D to provide prompt written notification to the R&D Committee of for-cause suspensions and terminations of IRB approved research projects and of any serious unanticipated problems involving risks to subjects or others and the resolution of those problems. This does not include expirations of IRB approval.

B. Notification to the Investigator

The IRB shall notify the Principal Investigator in writing of its determinations as determined in Section V, FO, 501. Copies of all correspondence between the IRB and the investigator will be filed in the appropriate research project file.

Regardless of the type of review (approved as exempt, expedited or reviewed at a convened IRB meeting), the investigator is notified in writing of the IRB's and R&D Committee's determinations.

The IRB shall notify the principal investigator in writing of suspensions or terminations and shall include a statement of the reasons for the IRB's actions. The terms and conditions of the suspension must be explicit. The investigator shall be provided with an opportunity to respond in person or in writing.

C. Notification to the Chief of Staff

The Chief of Staff will be notified of suspensions, regarding lapses in continuing review consistent with the policy outlined in Section VI, RR, 602, E. The RACC is responsible for notifying the Chief of Staff in these instances.

It is the responsibility of the IRB Chairperson and/or the ACOS/R&D to provide prompt written notification to the Chief of Staff of for-cause suspensions and terminations of IRB approved research projects and of any serious unanticipated problems involving risks to subjects or others and the resolution of those problems.

D. Notification to the Medical Center Director

It is the responsibility of the IRB Chairs and/or the ACOS/R&D to provide prompt written notification to the Medical Center Director of for-cause suspensions and terminations of IRB approved research projects and of any serious unanticipated problems involving risks to subjects or others and the resolution of those problems. This does not include expirations of IRB approval.

E. Notification to the Regulatory Agencies

It is the responsibility of the IRB Chairs and/or the ACOS/R&D to provide prompt written notification to relevant Federal agencies, including ORO, OHRP, and FDA (for FDA-regulated research) of for-

cause suspensions of IRB approved research projects and of any serious unanticipated problems involving risks to subjects or others and the resolution of those problems. The PVAMC will report information at the discretion of the R&D Committee, regarding the protection of human subjects in research consistent with the ORO Memorandum dated November 12, 2003. This does not include routine study closures, study completions or expirations in IRB approval.

Information that may be reported includes: 1) findings of unanticipated problems involving risks to subjects or others. Adverse events that a) cause harm or pose risk of harm to research participants and for which an IRB takes substantive corrective action, i.e. substantive change(s) to the protocol and/or consent form, or restrictions, suspension or termination of study or investigator participation, or b) involve the death of healthy volunteers participating in research and 2) for cause suspensions and terminations (e.g. associated with unexpected harm).

FO 506

Appeal of IRB Determinations (38 CFR 16.109(d))

The IRB shall provide the PI with a written statement of its reasons for disapproving or requiring modifications in proposed research and shall give the PI an opportunity to respond. This correspondence will be provided to the PI within a reasonable time frame for items reviewed outside of a convened meeting. The PI or appropriate designee shall respond in writing for those items requiring a signature (such as a revised initial review questionnaire), but may submit other revisions electronically to the IRB Coordinator. A time frame and format for response will be provided on the IRB correspondence based on the nature of the requested response.

In such cases as there is a dispute between the IRB and the PI regarding required modifications to the protocol or other parts of the IRB application which can not be amicably resolved between the parties involved, an appeal to the R&D Committee may be made by either the PI or the IRB.

The R&D Committee may organize a meeting with the individuals noted above to discuss the issue at hand, and will arrange further meetings with the PI and the IRB or designee as needed. The R&D Committee will facilitate the discussion between the PI and the IRB. Final recommendations for approval remain under the purview of the IRB that made the original determinations that are appealed, i.e., the appeal will not be reviewed and considered by the other IRB. However, the R&D Committee may want to comment on the process and make recommendations to the IRB for future protocols similar to the one under appeal.

FO 507

Individualized IRB Consultations

Individuals who have questions regarding Institutional Review Board policies and procedures, e.g. questions involving whether or not a project is considered human subjects research and whether it should be submitted to the IRB for review and approval, should direct the question in writing to the IRB Coordinators. Once received, the IRB Coordinators will consult with the IRB Members and Chair, if necessary, to address an individual's questions. Investigators should not contact the IRB Members or Chair directly with questions related to IRB policies and procedures. It is not the policy of the PVAMC IRB to provide curbside consults (personal consultations) to individual investigators and medical staff.

If an IRB Member or Chair receives a request for consultation, this request should be forwarded to the IRB Coordinators for a documented response to the individual's questions.

FO 508

Audits of Research Protocols or Study Procedures

The IRB or designee may audit a research protocol or study procedures at any time for any reason. The IRB will maintain documentation that such an audit occurred, the result of the audit, and, if a response was required from the principal investigator or other designated person, the response generated.

Continuous Quality Improvement audits are conducted consistent with the HRPP Policy & Procedure No. 9, “Continuous Quality Improvement in the Human Research Protection Program” (Appendix Q).

FO 509**Electronic Submission of Informed Consent Forms**

The Research Service office will accept informed consent forms electronically at the time of IRB submission. If, at the time of review, the IRB requests that only minor typographical and/or grammatical changes need to be made to the informed consent form, the IRB staff may make these minor changes and generate an IRB approval. The IRB meeting minutes and correspondence to the principal investigator will reflect that the IRB staff have made the minor typographical and/or grammatical changes to the informed consent form and that the changes may be viewed on the “tracked changes” copy. Both a clean, stamped copy of the informed consent form, as well as a copy with the “tracked changes” (i.e. highlighted with MS Word function) will be provided to the principal investigator and filed in the Research Service’s research project file. If the principal investigator agrees with the changes, the IRB approved consent form may be used immediately, without further discussion. If changes have been made that the investigator does not agree with, correspondence should be submitted to the IRB explaining why the investigator does not agree with the changes and offering alternate phrasing.

RR 601

Initial Review by the Convened IRB (38 CFR 16.103(b)(4) and 21 CFR 56.108-109)

Unless determined to be exempt from IRB review, all human subjects research conducted at the PVAMC facility by PVAMC employees or agents or otherwise under VA auspices must be reviewed and approved by the IRB and by the R&D Committee prior to initiation. No human subject research may be initiated or continued at the PVAMC by employees or agents without the appropriate approvals of both the IRB and R&D Committee.

Both the IRB and R&D Committee must grant final approval to a proposed research project prior to initiation of the research project. An investigator must have received all final written approvals from all applicable subcommittees and the R&D Committee, prior to beginning the research.

During initial review, the IRB reviews proposals for research involving human subjects submitted by investigators. The purpose of initial review is to ensure compliance with existing Federal laws and regulations for the protection of human subjects. The IRB has the authority to disapprove, require modifications to secure approval, and approve research protocols based on its consideration of the risks and potential benefits of the research, and whether or not the rights and welfare of human subjects are adequately protected.

At the meeting the IRB, led by the primary reviewer(s), will: (1) review and discuss the proposal, (2) provide an assessment of the soundness and safety of the protocol, (3) make recommendations for protocol and informed consent revisions and (4) take appropriate action(s) regarding approval. The Principal Investigator may attend the meeting at the invitation of the IRB. The Principal Investigator may answer questions or provide additional clarification, but may not be present during deliberations or voting on the proposal.

If a reviewer is absent from the meeting a new reviewer may be assigned, as long as the new reviewer has reviewed the requisite materials prior to the meeting. An absent reviewer can submit their written comments to be read at the meeting, as long as another reviewer is present to serve as a primary reviewer.

At the time of initial review, the IRB will determine the frequency of continuing review of the research, designating an interval that is appropriate to the degree of risk of the research project. Members will use the IRB Primary Reviewer Form as noted in Appendix E to assist in determining the risk level and ensuring that the information provided meets appropriate guidelines.

Members of the IRB vote upon the recommendations made by the reviewers according to the criteria for approval in Section VI, RR, 603 & 604. A majority of voting members present must vote in favor of an action for that action to be accepted by the IRB. Only regular members, or in their absence alternate member(s), may vote. A record of the vote will be recorded in the minutes, as indicated in Section V, FO, M.

A. Initial Review Process: These guidelines should be followed in the conduct of the initial review of all proposals:

The primary reviewers should lead the discussion by presenting their findings and recommendations resulting from the review of the application materials.

1. Review of the Protocol: The proposed protocol will be reviewed by the primary reviewers and the abstract will be reviewed by the full IRB to determine if the research project meets the criteria for approval in Section VI, RR, 603 & 604. Recommendations for protocol modifications will be made by the primary reviewers and voted upon. The reviewer should complete the IRB Primary Reviewer Summary to document that each of the specific criteria for approval have been met. All IRB Primary Reviewer Summaries will then be filed in the appropriate research project file.
2. Review of the Informed Consent Form: All IRB members are provided a copy of the proposed informed consent form. The IRB will determine if it meets the criteria outlined in Section VIII, IC, 801 N-P. The IRB may approve consent forms with minor changes only at the meeting. Such changes will be reviewed and approved by the primary reviewer and/or IRB Chair. If substantive modifications are required the consent form must be reviewed again by the full IRB prior to approval.
3. Review of the Request for Waiver of Informed Consent Requirements and Authorization to Release Medical Records or Health Information:
All IRB members are provided a copy of the request for waiver of informed consent and HIPAA Authorization form, if applicable. The IRB will determine if it meets the criteria outlined in Section VIII, IC 801, L or M. The IRB may approve the request for waiver of informed consent requirements and HIPAA Authorization with minor changes only at the meeting. Such changes will be reviewed and approved by the primary reviewer and/or IRB Chair. If substantive modifications are required the form must be reviewed again by the full IRB prior to approval.
4. Review of the Initial Review Questionnaire:
All IRB members are provided a copy of the proposed IRQ. The IRQ captures essential information required for the IRB review and approval. The IRB primary reviewers are responsible for ensuring that this form is completed appropriately and in its entirety. Any concerns, regarding the IRQ will be commented on at the convened IRB meeting and documented in the correspondence to the principal investigator.
5. Review of the IRQ Attachments:
All IRB members are provided a copy of the other IRB forms complementing the IRQ. These forms may include the: Investigational Device Information Record, Investigational Drug Information Record (VA Form 10-9012), FDA Form 1572, Human Biological Specimens Questionnaire, Human Biological Specimens Memo of Understanding and Conflict of Interest in Human Research Form. Any concerns, regarding the IRQ attachments will be commented on at the convened IRB meeting and documented in the correspondence to the principal investigator.
6. Review of the HIPAA Forms:
All IRB members are provided a copy of any submitted HIPAA forms complementing the IRQ. These forms may include the: Application for a Partial Waiver of Authorization for

Screening/Recruitment Purposes, and the De-Identification Certification Forms. Any concerns, regarding the HIPAA Forms will be commented on at the convened IRB meeting and documented in the correspondence to the principal investigator.

7. Protection of Vulnerable Populations: If the research study proposes to recruit vulnerable populations of subjects, the IRB will review, discuss, and/or require modification to secure approval of the investigator's plan for minimizing undue influence on vulnerable subjects in accordance with Section VI, RR, 603, I.
8. Protection of Privacy and Confidentiality:
The IRB will determine whether there is an appropriate plan to protect the confidentiality of research data that may include coding, removal of identifying information (in order to protect personally identifiable information), limiting access to data, use of Certificates of Confidentiality, waiver of documentation of consent, physical or computerized methods for maintaining the security of stored data, or other effective methods. The IRB will evaluate the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research and the effectiveness of the proposed methods. The IRB will also determine whether methods used to identify and recruit and obtain information about potential participants protect subject privacy and confidentiality and whether the informed consent form adequately discloses the risks to privacy and confidentiality. The IRB may require that the investigator obtain a Certificate of Confidentiality if it determines that special protections are needed to protect subjects from the risks of investigative or judicial processes. The IRB will ensure that the required language for a valid authorization to release health information under HIPAA is included as part of the informed consent document(s). The IRB may waive the requirement for an authorization or may alter the form or content of the authorization as permitted by HIPAA and described in the HRPP Policy & Procedure No. 6, "Health Insurance Portability and Accountability Act (HIPAA) Human Subjects Research Policies and Procedures." These actions and their justification will be documented in the IRB minutes.
9. Conflict of Interest:
The IRB will review the conflict of interest questions on the Initial Review Questionnaire and if applicable, the Conflict of Interest in Human Research Form submitted by the Principal Investigator to identify potentially significant financial or non-financial conflicts of interest. If a conflict of interest has been identified, the IRB will make recommendations to the R&D Committee regarding methods to minimize, manage, monitor and/or eliminate potentially significant financial or non-financial conflicts of interest. Please refer to the Human Research Protection Program Policy & Procedure No. 5, "Conflict of Interest in Human Research," for more information, regarding how conflicts of interest are identified and managed.
10. Payment to subjects:
The IRB will determine whether proposed payments to subjects are appropriate and do not represent an undue influence on the trial subjects as determined in Section VI, RR, 604, F.
11. Recruitment Incentives:
The IRB will determine whether or not recruitment incentives to the investigator from a sponsor may create undue influence to recruit patients for a study and are reasonable in

relation to the work being performed as described in Section VI, RR, 604, F.

12. Review of Advertisements and Recruitment Methods:

Members will review the content of all submitted proposed advertisements, proposed recruitment methods, and all other written material to be provided to subjects.

All IRB members are provided a copy of any submitted advertisements. The primary reviewer may complete the Advertisement Primary Reviewer Checklist to document that each of the criteria in Section VI, RR, 604, D for approval have been met. All completed Advertisement Primary Reviewer Checklists will then be filed in the appropriate research project file.

13. Review of Safety Monitoring:

For studies that are blinded, have multiple sites, recruit vulnerable populations, or employ high-risk interventions, a general description of the data and safety monitoring plan must be submitted to the IRB as part of the proposed work. This plan should contain procedures for identification and reporting of adverse events. For studies that have a Data Safety Monitoring Board (DSMB), the research plan must make adequate provisions for monitoring the data collected to ensure the safety of subjects.

14. Placebo-Controlled Studies:

At the time of initial review, Principal Investigators should complete the PVAMC Checklist for Placebo-Controlled Studies, if their study involves a placebo-controlled design. The completed checklist will be distributed to the IRB primary reviewers. During the review and consideration of the research project and placebo-control study design, the convened IRB will discuss and complete the PVAMC Checklist for Placebo-Controlled Studies.

B. Review of Proposed Foreign Research

The PVAMC IRB recognizes the crucial problems of oversight in the conduct of scientific research in foreign countries and will consider such research in the most rare of circumstances.

The PVAMC IRB will review all requests from principal investigators related to foreign research. However, the IRB also recognizes the problems that exist with oversight of such foreign research and the IRB recognizes that such research requests will be rare and most typically under the oversight of the National Institute of Health (NIH) or other federal regulatory agency. Even in these rare cases where research may be conducted in a foreign country, the principal investigator will be required to demonstrate approval of a federal agency for the research study, and demonstrate local foreign approval.

C. Approval of Modifications Required to Secure Approval

In cases where research projects are approved pending minor modification at the time of initial review, investigators are given a three-month deadline to submit the required modifications to the IRB.

If the PI has not replied to the contingencies after three-months, the IRB Coordinators will contact the PI to remind them about their contingencies and to determine whether or not the PI will be submitting the contingencies or terminating the study.

This deadline may be extended up to another three months for a total of six months, provided that the investigator keep the Research Service office informed of the status of the protocol. After the six month period, the investigator will receive a warning that if the requested modifications are not submitted within the next 7 days, the protocol will be administratively withdrawn. If the project is administratively withdrawn, this will require the investigator to submit the study as a new protocol for full review if they intend to pursue IRB approval

The IRB will consider exceptions to this policy in extraordinary circumstances that may be out of the investigator's control. These circumstances may include: awaiting word regarding funding status, or awaiting changes being made by the sponsor, which may extend the time that an investigator needs to make required modifications.

RR 602**Ongoing Review****A. Review of Amendments and Changes in IRB Approved Research Procedures and Consent Forms**

The IRB must conduct a review of all proposed modifications to IRB approved research projects, including even minor changes and modifications to informed consent forms. The IRB must approve any changes prior to the implementation of the proposed changes, except when necessary to eliminate apparent immediate hazards to the subject. The proposed modifications should be submitted to the Research Service office with the "Project Revision/Amendment Form (PR/AF- Appendix C)." These modifications will be reviewed by the Primary Reviewer System, presented to and voted on at the full IRB at the convened meeting. The Primary Reviewer will receive the "PR/AF," most current IRB approved consent form, documents that include the proposed changes and the current IRB approved document that is up for review of proposed changes, if one exists. A mechanism in place to ensure that these changes are reported promptly and not initiated without IRB approval, except in the above stated circumstance, include verifying at the time of continuing review that no changes have been made to the research project without prospective IRB approval.

B. Violations/Deviations to IRB Approved Research Protocols**1. Review of Violations/Deviations from the IRB Approved Protocol**

A violation/deviation can be any unplanned or unapproved research activity that is committed or omitted contrary to the terms of the IRB-approved research.

The IRB presumes that what is occurring in the implementation of protocol procedures is consistent with what was approved by the respective committees. However, the committees recognize that deviations and exceptions to approved IRB protocols may occur. A deviation is defined as any change to the IRB approved protocol and/or procedures without prior IRB notification and approval (modification). The cause of the deviation may be within the investigator's control (e.g. change a protocol procedure or medication), or a deviation may not be in the control of the investigator (e.g. a subject fails to show-up for a procedure defined in the protocol). All changes to the IRB approved protocol must have prior approval of the IRB. Any non-approved change is a deviation. It is the responsibility of the Principal Investigator to notify the IRB of all protocol deviations.

2. In regards to violations/deviations, the FDA regulations at 21 CFR 56.108 (a) (3-4) state that, "In order to fulfill the requirements of the regulation, each IRB shall:

- (a) Follow written procedures:
 - (3) For ensuring prompt reporting to the IRB of changes in research activity and
 - (4) For ensuring that changes in approved research, during the period for which IRB approval has been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects."

3. Major Protocol Violations/Deviations

Major deviations are deviations that meet the following criteria:

- (a) exposed subjects to potential increased risk or,
- (b) compromised the integrity of the entire study.

Such major deviations must be reported **within 10 working days** after the deviation becomes known. The PI should submit an explanation of the circumstances that led to the deviation, a description of steps taken to address the problems resulting from the deviation, and a plan for assuring that similar deviations will not occur in the future.

4. Minor Protocol Violations/Deviations

All other deviations, which do not meet the criteria defined above, will be considered minor deviations from the approved protocol and should be summarized and reported to the IRB at the time of continuing review or project termination. The minor deviations, which are reportable to the IRB at the time of continuing review form or project termination will be reviewed and if necessary, appropriate action will be taken by the IRB.

C. Review of Non-Compliance in Human Research

The IRB will address any research-related complaints and allegations of non-compliance with HRPP and IRB policies raised against a principal investigator or research staff. Such allegations will be brought to the IRB by the Chair or RACC. The IRB will determine the validity of complaints and allegations brought to its attention by the RACC and make a recommendation for remedial action. The IRB will document in the IRB meeting minutes, the discussion, deliberation and final recommendation to the R&D Committee.

Please see Human Research Protection Program: Policy & Procedure No. 3, "Complaints and Allegations of Non-compliance in Human Research," in Appendix K for more details.

D. IRB Continuing Review

(38 CFR 16.103(b)(4) and 109(e))

The IRB will conduct substantive and meaningful continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. The IRB reserves the right to change the approval period at any time for any reason. The IRB approval period for research may not extend more than 365 days from the time that the convened IRB voted on approval, or approval pending minor modifications, or the date of approval resulting from the expedited review process if expedited review was performed.

Investigators are notified in writing of the approval date and the expiration date at the time of final initial IRB approval. The IRB continuing review date is set approximately two months prior to the expiration of IRB approval.

The IRB continuing review materials will include all applicable IRB submission materials as noted in Section V, FO, 504, B. The IRB employs the Primary Reviewer System at the time of continuing review.

1. During the continuing review, the IRB takes the following into consideration:

- (a) changes to the research;
- (b) adverse event reports; safety reports, including IND, IDE and MedWatch;
- (c) reports of unanticipated problems, involving risk to subjects, and if available data safety monitoring reports;
- (d) protocol violations and/or deviations;
- (e) overall investigator non-compliance, including non-compliance with IRB requirements for frequency of periodic continuing review; and

- (f) informed consent document(s). The IRB shall determine whether or not the currently approved or proposed consent document is still accurate and complete, and whether or not any significant new findings that may relate to the subject's willingness to continue participation are provided to the subject in accordance with HHS regulations at 45 CFR 46.116(b)(5).
2. Approximately one month prior to the IRB continuing review date, the IRB Coordinator(s) send via e-mail a notification to the Principal Investigator that the IRB continuing review is scheduled and the continuing review form that needs to be completed. In effect, the investigator will receive materials to submit for the continuing review approximately 90 days before the current approval for the research project expires. Investigators are asked to submit the materials in time for the next month's meeting, allowing for review approximately 60 days before the protocol's expiration date. Investigators that do not respond by the date the continuing reviews are due are sent an e-mail reminder from the IRB Coordinator(s). If the material is not submitted in a timely manner and it is not possible to get the materials to the IRB meeting prior to the approval expiration date, the study will automatically be suspended, per the procedures outlined in Section VI, RR, 602, E.
 3. Studies that meet expedited review criteria at the time of initial review, may meet expedited review criteria for continuing review, and this determination will be made by the IRB Chairperson or the Chair's qualified designee.
 4. A research project that is contingently approved at the time of continuing review cannot enroll new subjects or access medical records after the research project's expiration date, unless the contingencies are met. The Principal Investigator must respond to the IRB contingencies by the date specified. If the Principal Investigator does not respond, s/he will receive a letter from the ACOS/R&D notifying the PI that s/he has violated the Investigator Assurances agreed to on the Initial Review Questionnaire. The IRB may administratively terminate the study.

E. Expiration of IRB Approval Period

(38 CFR 16.109(e))

Per federal regulations, the IRB approval period for research may not extend more than 365 days from the time that the convened IRB voted on approval, or approval pending minor modifications, or the date of approval resulting from the expedited review process if expedited review was performed.

The regulations permit no grace period after approval expiration. Research that continues after the approval period expires is research conducted without IRB approval. If the continuing review does not occur within the timeframe set by the IRB, the research is automatically suspended. A research project may only continue if the research project is approved or contingently approved (approved with minor modifications), within 365 days from the time that a convened IRB voted on approval, approval pending minor modifications, or the date of the expedited review process if expedited review was performed.

Per VHA ORD policy, if the continuing review does not occur within the timeframe set by the IRB, then, the research is automatically suspended. The Research Service is responsible for promptly notifying the PI of the suspension.

If research participants are currently enrolled in the research project and their participation is ongoing, once notified of the suspension the PI must immediately submit to the IRB Chair a list of research subjects for whom suspension of the research would cause harm. Enrollment of new subjects cannot occur and continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB or IRB Chair, in consultation with the Chief of Staff (COS), finds that it is in the best interest of individual subjects to do so. The Research Service will notify the COS of any studies that have been suspended due to expiration of the IRB approval period.

If the study is FDA-regulated, the COS and IRB Chair must follow FDA requirements in 21 CFR 56.108(b)(3) in making their decision.

The sponsoring agency, private sponsor, ORD, ORO, or other Federal agencies must be informed, as appropriate.

Once suspended, IRB review and re-approval must occur prior to re-initiation of the research. If the study approval has lapsed more than 2 months by the time of approval expiration, the PI must submit a new application to the IRB for review and approval. If the study approval has lapsed less than or equal to 2 months by the time of approval expiration, the items requested at the time of continuing review may be reviewed for consideration of continued IRB approval.

The Research Service will notify the COS as to whether or not the PI will be terminating or requesting re-approval of the research project by the IRB.

Once the PI submits the required information, it will be reviewed as appropriate by the IRB. Principal investigators who fail to comply with continuing review timelines may be suspended from conducting research. This will be evaluated on a case-by-case basis.

F. Interim Reports

If the IRB determines that a study requires an Interim Report, the investigator may be asked to submit a Continuing Review Questionnaire by a specified date, upon enrollment of a specified number of subjects, or upon reaching a specified point in the study. If interim reports are not received as scheduled, the IRB may suspend enrollment until reports are reviewed. The IRB will review the Continuing Review Questionnaire at a convened meeting, and may require modifications or take other actions within its authority. During a review of interim reports, the following must be considered:

1. Proposed changes (if any) to the research study and any accompanying changes to the informed consent form.
2. Adverse event reports
3. Reports of unanticipated problems impacting the risks to subject
4. Summary of data safety monitoring board (DSMB) reports (if available)
5. Review of any protocol violations or deviations
6. Overall investigator compliance

G. Review of Reports of Unanticipated Problems involving risks to patients or Adverse Events (21 CFR 312.66)

This also includes Safety Reports, IND, IDE and Medwatch Reports

All investigators conducting research as employees or agents in the PVAMC are required to notify the IRB promptly of any adverse events (AEs) or unanticipated problems involving risks to

subjects or others that occur in research conducted at the PVAMC or by PVAMC employees or agents, or under VA auspices. Principal Investigators are also required to report promptly to the IRB any adverse event (AE) that is reported to ORO, the FDA and/or the sponsor in accordance with FDA requirements.

Principal Investigators should complete an OHSU/PVAMC Adverse Event Report Form for all adverse events occurring for studies approved by the IRB. The form is available online at: http://www.ohsu.edu/ra/irb/docs/sample_forms/aeform.doc. A copy of this form is included in Appendix F. The form is one which tracks all adverse events which occur over the life of a protocol to allow tracking and enhanced monitoring of the adverse events.

1. **Types of adverse events that must be reported**

- ALL deaths must be reported for interventional studies, **regardless of cause of death**, for all subjects who received their last treatment less than 30 days ago.
- Also report any of the following experiences for all subjects who received their last treatment less than 30 days ago:
 - (a) All serious adverse events/experiences, expected (described in the consent) or unexpected. Serious experiences are those that are fatal, life-threatening, permanently disabling, result in hospitalization or prolongation of existing hospitalization, or result in a congenital anomaly or birth defect, or important medical events that may not result in one of the above but that require treatment (allergic reactions, seizures, etc.) [21 CFR 312.32(a)(1)]. Cancers, medication overdoses, and emotional harms are also considered serious.
 - (b) ALL unexpected adverse events/experiences [21 CFR 56.108(b)(1)] EXCEPT for those that are not serious (see above), do not require medical intervention (are self-resolving) and have occurred in isolation (not more than one time to the investigator's knowledge).

2. **Timeline for reporting adverse experiences**

Experiences should be reported for subjects still enrolled in the study or subjects who received their last treatment (e.g., medication dose, blood draw, etc) less than 30 days ago.

(a) **24 Hours**

Deaths must be reported within *24 hours for subjects at OHSU or the PVAMC, or within 24 hours from the time you are notified of experiences at other centers.*

Acceptable forms of meeting this 24-hour timeline are:

- Email: PVAMC-IRB@med.va.gov
- Fax: 503-273-5351

The contents of the email or fax must include:

- PI's name,
- VA IRB ID#,
- Study title,
- Date of the experience,
- Subject identifier, and

- a brief description of the experience.

If a Principal Investigator uses email or fax to file an abbreviated report, the Principal Investigator must nevertheless submit a full written report as soon as possible.

(b) **10 Working Days**

All other reports should be submitted within *10 working days of the experience if at OHSU or the PVAMC, or within 10 working days of notification for experiences at other sites.*

3. **Applicability**

These guidelines apply to adverse events/experiences occurring at any site. However, for large multi-site clinical trials, involving a coordinating center, adverse events/experiences occurring at other sites, may be reported consistent with the study sponsors coordinating center policy. However, in the case of an adverse events/experiences occurring at Oregon Health & Science University, these should be reported directly to the PVAMC IRB.

4. **Review by the IRB**

The IRB Chairs perform an initial review of all adverse events and unanticipated risks to a human subject either on site at the PVAMC or at a distance site as received by the Principal Investigator and determine whether or not immediate action is necessary in regards to patient safety.

Immediate action may include calling a special meeting of the IRB to determine whether or not patients already enrolled in the study need to be informed of this new unexpected adverse outcome that has occurred, as well as to determine the proper change(s) to the informed consent form that will need to be made to inform patients of this heretofore unanticipated risk. In addition, at the special meeting of the IRB (if one is deemed necessary), it will be determined whether the study should be stopped until further information related to this unanticipated risk has been obtained or whether the study can continue with proper notification of enrolled patients and with proper changes to the existing informed consent form. If an emergent issue arises and a special meeting of the IRB may not be convened, the IRB Chair may take immediate action.

If immediate action is not required, a primary reviewer will be assigned to review and present the adverse event(s) at the next convened IRB meeting. The results of the review will be noted in the IRB meeting minutes.

The IRB member that conducts the review of the adverse event evaluates and documents if the adverse event changes the risks to subjects for the study from the risks that are previously outlined in the current informed consent form. The IRB reviewer makes and documents a recommendation to the convened IRB, based on his/her review, whether or not the research may continue, may continue with modifications, must be suspended or must be terminated. If the research may continue with modifications, the IRB reviewer documents the modifications needed and whether or not all of the research subjects currently enrolled should be re-consented. This determination is discussed at a convened IRB meeting and the IRB then decides on the proposed action.

5. Notification to Relevant Agencies

The IRB Chairs or ACOS/R&D shall provide prompt written notification to the PVAMC's R&D Committee and to relevant Federal agencies, including ORO, OHRP, and FDA (for FDA-regulated research) of any serious unanticipated problems involving risks to subjects or others, and of the resolution of those problems. The PVAMC will report information at the discretion of the R&D Committee, regarding the protection of human subjects in research consistent with the ORO Memorandum dated November 12, 2003.

Information that may be reported includes: 1) findings of unanticipated problems involving risks to subjects or others. Adverse events that a) cause harm or pose risk of harm to research participants and for which an IRB takes substantive corrective action, i.e. substantive change(s) to the protocol and/or consent form, or restrictions, suspension or termination of study or investigator participation, or b) involve the death of healthy volunteers participating in research and 2) for cause suspensions and terminations (e.g. associated with unexpected harm).

H. Review of Adverse Event or Safety Reports in Sponsored or Cooperative Group (Multi-center) Projects

The IRB review of such reports is handled in the same manner as internal reports of unanticipated problems or adverse event as detailed in Section VI, RR, 602, G above, unless otherwise stated in the research project and approved by the IRB.

I. Review of Data and Safety Monitoring Board (DSMB) Reports

Data and Safety Monitoring Board Reports should follow the guidelines noted above for non-fatal events. The IRB Chairs will perform an initial review of all reports, and take action as needed, based on the nature of the report. If immediate action is not needed, a primary reviewer will be assigned for review at the next IRB meeting, and results will be noted in the IRB minutes.

When DSMBs are used, as indicated on the IRQ, the IRB may rely on a current statement from the DSMB indicating that it has reviewed study-wide AEs, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to ensure that its ongoing review is substantive and meaningful.

J. Significant New Findings

During the course of research, significant new knowledge or findings about the medication or test article and/or the condition under study may develop. Since the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the IRB may require during the ongoing review process that the Principal Investigator contact the currently enrolled subjects to inform them of the new information. The IRB will communicate this to the Principal Investigator. The informed consent should be updated and the IRB may require that the currently enrolled subjects be re-consented, acknowledging receipt of this new information and for affirming their continued participation.

K. Review of Study Termination Reports

The IRB reviews and acknowledges study termination reports upon receipt from the investigator. Investigators are to submit a notice of study termination to the IRB Coordinator upon completion of the research project. The notice should be submitted on the "Research Project Termination Report" form. However, if at the time the continuing review paperwork is submitted to the IRB, the CRQ indicates that the study is terminated, then it is reviewed as a research project termination.

L. Suspension or Termination of IRB Approval of Research

(38 CFR 16.113)

All investigators conducting research as employees or agents in the PVAMC are required to notify the IRB promptly of any serious or continuing non-compliance with applicable regulatory requirements or with the determinations of the IRB.

The IRB may vote to suspend or terminate approval of research not being conducted in accordance with IRB or regulatory requirements or that has been associated with unexpected problems or serious harm to subjects.

The IRB shall notify the principal investigator in writing of such suspensions or terminations and shall include a statement of the reasons for the IRB's actions. The terms and conditions of the suspension must be explicit. The investigator shall be provided with an opportunity to respond in person or in writing.

Where the IRB Chairperson determines that such action is necessary to ensure the rights and welfare of subjects, the Chairperson may require an immediate, temporary suspension of enrollment of new subjects or of continued participation of previously enrolled subjects, pending review of the situation by the convened IRB.

It is the responsibility of the IRB Chairperson and/or the ACOS/R&D to provide prompt written notification to the R&D Committee, the Chief of Staff and the Medical Center Director as well as to relevant Federal agencies, including ORO, OHRP, and FDA (for FDA-regulated research) of for-cause suspensions and terminations (e.g. associated with unexpected harm and research not being conducted in accordance with the IRB's requirements) of IRB approved research projects. Routine study closures, expirations in IRB approvals, or study completions are not to be reported to these agencies.

RR 603**Required Criteria for IRB Approval of Research**

The IRB shall determine the following during the initial and continuing review and approval of research, as stated in the Department of Veterans Affairs, Department of Health & Human Services, and Food & Drug Administrations regulations.

A. Risks to Subjects

(38 CFR 16.102(i) and 110)

The IRB must consider the overall level of risk to subjects in evaluating proposed research during the initial and continuing review of the research. The IRB identifies the risks to the subject. These risks are clearly identified in the informed consent form. The IRB determines the level of risk of a protocol by evaluating the nature of several types of risk, including but not limited to physical, psychological, and social/economic harms that could result from participation in the research. The IRB also evaluates the probability of the occurrence of a risk, as well as the severity of each potential risk in order to qualify each protocol as less than minimal, minimal, moderate or high risk. The IRB determines the interval for continuing review based on the level of risk of the research project.

The regulations require that the IRB distinguish research that is greater than minimal risk from research that is no greater than minimal risk, when considering proposals for expedited review and for vulnerable populations. However, the IRB assesses the risk/benefit in all research protocols.

The IRB uses the following criteria for determining whether or not the risks to the subjects are minimal: under VA regulations at 38 CFR 16.102(i), “**minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

Generally, research projects that may be considered high risk involve high-risk invasive procedures, a Phase I or II clinical trial, investigational drugs, or a significant risk investigational device.

B. Risks Minimized

(38 CFR 16.111(a)(1))

To approve research, the IRB must determine at the time of initial and continuing review that risks are minimized by (1) using procedures that are consistent with sound research design and (2) do not expose subjects to unnecessary risks. Whenever appropriate, the research should utilize procedures that are already being performed on the subjects for diagnostic or treatment purposes.

The IRB examines the research plan, including research design and methodology, to determine that there are no obvious flaws that would place subjects at unnecessary risk. This includes the risk that the research is so poorly designed or is so lacking in statistical power that meaningful results cannot be obtained.

The IRB also considers the professional qualifications and resources of the research team as indicated on the IRQ. The PI must designate all research staff on the IRQ, including co-investigators, collaborators, and study coordinators. In addition, in all studies that are outside the PI's medical specialty, the PI must designate a co-investigator or collaborator with expertise in the relevant medical

specialty being studied. This co-investigator or collaborator will be in charge of all patient safety issues related to the checking of all laboratory/study testing in the research, following all laboratory/study results and communicating all moderate or severe results to the study participant, the study participant's primary care and specialty physicians, and assuring the accurate recording of all relevant laboratory/studies in the patient's electronic medical record.

Clinicians are expected to maintain appropriate professional credentials and licensing privileges. The IRB reserves the right to request additional information from investigators and participating physicians, such as curricula vitae, to assure that the qualifications of the research team are appropriate for the proposed study. Additional research staff working physically at the VA and having direct contact with VA patients and/or their identifiable data or human biological specimens, must also be credentialed consistent with VA Office of Research & Development guidelines.

The Research Service staff verifies that the individuals listed on the IRQ that will be working on the research project at the VA have completed the appropriate credentialing requirements, consistent with HRPP Policy & Procedure No. 10, Credentialing of Personnel Involved in Human Studies Research (Appendix S).

C. Risks Reasonable Relative to Anticipated Benefits

(38 CFR 16.111(a)(2))

To approve research, the IRB must determine at the time of initial and continuing review that the risks of the research are reasonable in relation to the anticipated benefits (if any) to subjects, and the importance of the knowledge that may reasonably be expected to result. This is determined at the time of initial and continuing reviews, as well as on an ongoing basis for other paperwork (such as amendments) submitted for each protocol. The IRB considers the following types of risks: physical, psychological, and social/economic and determines the level of risks of the research. Probable individual and societal benefits of the research are also considered.

The IRB develops its risk/benefit analysis by evaluating the most current information about the risks and benefits of the interventions involved in the research, in addition to information about the reliability of this information. The IRB should consider only those risks that result from the research, and should not consider the long-range effects (e.g., public policy implications) of applying the knowledge gained in the research.

D. Equitable Selection of Subjects

(38 CFR 16.111(a)(3))

The IRB determines by viewing the IRQ, protocol and other research project materials that the selection of subjects is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not provide adequately for the equitable selection of subjects or has not provided an appropriate scientific and ethical justification for excluding classes of person who might benefit from the research.

This is the concept of "Justice" from the Belmont Report. In making this determination, the IRB evaluates: the purposes of the research; setting in which the research occurs; scientific and ethical justification for including vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons; the scientific and ethical justification for excluding classes of persons who might benefit from the research; and the inclusion/exclusion criteria.

E. Circumstances of Informed Consent Requirements

To approve research, the IRB must determine that legally effective informed consent shall be sought from each prospective subject or the subject's legally authorized representative (see 38 CFR 16.116), unless informed consent requirements can be waived or altered under VA regulations. All informed consent forms and any such waiver must be consistent with applicable Washington and Oregon state law regarding content and participation in research.

Informed consent may only be sought under circumstances that provide the subject (or the legally authorized representative) with sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence (38CFR16.116). These circumstances are described in Section VIII, IC, 801.

F. Documentation of Informed Consent

(38 CFR 16.117)

To approve research, the IRB must determine that informed consent shall be appropriately documented, in accordance with, and to the extent required by VA, FDA, the Common Rule regulations and applicable state and local regulations. Requirements for informed consent and documentation are described in Section VIII, IC, 801, C.

G. Review of Plans for Data and Safety Monitoring

(38 CFR 16.111 (a)(6))

To approve research, the IRB determines that, where appropriate, the research plan makes adequate provision for monitoring the data to ensure the safety of subjects. For research in which risks are substantial, the IRB may require a general description of the data and safety-monitoring plan to be submitted to the IRB as part of the proposal. This plan should contain procedures for reporting adverse events (AEs).

In general, it is desirable for a Data and Safety Monitoring Board (DSMB) to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable subjects, or employs high-risk interventions. For some studies the National Institutes of Health (NIH) require a DSMB. The IRB has the authority to require a DSMB as a condition for approval of research where it determines that such monitoring is needed.

When DSMBs are utilized, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has and will continue to review study-wide AEs, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB.

H. Privacy of Subjects and Confidentiality of Data

(38 CFR 17.33(a) and (b))

The IRB requires that subjects' confidentiality be strictly maintained. The IRBs serve as the Privacy Board for Research at the Portland VA Medical Center and abides by the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and the HRPP Policy & Procedure No. 6, located in Appendix N. The IRB recognizes the importance of protecting subject confidentiality, and carefully evaluates each protocol for the confidentiality measures taken. Only those authorized by the IRB, which may include the Principal Investigator, Co-Investigator and Research Assistant(s), etc., shall be allowed access to individually-identifiable patient information. Individuals must have prior approval

by the IRB before receiving individually identifiable patient data for research purposes. This may include requiring such measures as a set of research codes rather than the use of individually identifiable information, linked to the patient through only one codebook maintained by the Principal Investigator.

At the time of initial review, the IRB ensures that the privacy and confidentiality of research subjects is protected. The IRB assesses whether there are adequate provisions to protect subject privacy and maintain confidentiality. The IRB does this through the evaluation of the methods used to obtain information: about subjects; about individuals who may be recruited to participate in studies; the use of personally identifiable records; as well as the methods to protect the confidentiality of research data. In some cases, the IRB may also require that a Certificate of Confidentiality be obtained to additionally protect research data. The principal investigator will provide the information regarding the privacy and confidentiality of research subjects at the time of initial review through the completion of the Initial Review Questionnaire, any necessary HIPAA Forms, research protocol, and/or other submitted materials. The IRB will review all information received from the PI and determine whether or not the privacy and confidentiality of research subjects is sufficiently protected. The IRB primary reviewers will complete the IRB Primary Reviewer Summary at the time of initial review documenting such determinations.

In reviewing confidentiality protections, the IRB shall consider the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed anonymizing techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

I. Additional Safeguards for Vulnerable Subjects

(38 CFR 16.111(b) and M-3, Part 1, Chapter 9.09(a)(8))

For additional information regarding vulnerable subjects, please review Section VI, RR, 605 & 606.

The IRB carefully reviews at its convened meetings studies, which include vulnerable subjects. The PVAMC considers the following subjects as vulnerable subjects minors (children), fetuses, prisoners, pregnant women, mentally impaired, or economically or educationally disadvantaged persons.

The IRB must be cognizant of the vulnerable nature of many VA human subjects. However, veterans are not as a whole considered a vulnerable population

At the time of initial review the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. The IRB may determine and require that, when appropriate, additional safeguards be put into place for vulnerable subjects, such as those without decision-making capacity. The IRB may require that someone other than the primary care provider conduct the informed consent session and that additional measures for evaluating capacity to consent be in place. The IRB carefully evaluates each protocol to determine if vulnerable subjects are included in the study population and what measures have been taken to protect them. This feature is included in the IRB Reviewer Checklist included in Appendix E.

To approve research, the IRB determines that, where appropriate, additional safeguards have been included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or

undue influence. This includes but is not limited to research with children (45 CFR 46 Subpart D), prisoners (45 CFR 46 Subpart C), pregnant women (45 CFR 46 Subpart B), persons with mental disabilities, or economically or educationally disadvantaged persons. The PVAMC does not conduct research with children, prisoners or fetuses and the PVAMC IRBs do not review research involving these vulnerable populations.

RR 604**Additional Considerations During IRB Review and Approval of Research****A. Implementing Flag Advisories in the Electronic Medical Record**

Research studies which the IRB recognizes as moderate and/or high risk may require that a Research flag be activated in the patient's CPRS electronic medical record. Studies that generally require a flag are those that are invasive, including studies requiring surgery and/or utilizing investigational drugs or significant risk investigational devices. Flags may also be applied to studies for which the IRB feels it is important for any medical staff member working with an enrolled patient know that they are participating in a research study.

The Research Service will activate an electronic flag advisory for any project which the IRB requires a flag, once the study has received initial approval from the IRB and R&D Committee. An electronic record flag advisory is an electronic record flag, which serves as an immediately identifiable alert that promotes safe, appropriate, timely and respectful patient care. The VA electronic medical record is programmed such that when patients with electronic record flags make scheduled or unscheduled visits to the medical center and clinics, the patient information display will show a screen with the established type of flag advisory highlight.

The IRB Coordinators will notify the Principal Investigator and study coordinator when the flag is ready to be applied. As patients are enrolled into the research protocol, the Principal Investigator will obtain a signed informed consent and enter the patient's name into the medical record flag advisory system. The PI is responsible for activating the research flag immediately following the informed consent process with a patient. The Research Service is responsible for de-activating the research protocol flag when the study is concluded. However, the Principal Investigator is responsible for de-activating the research flag if a patient withdraws or participation ends prior to the termination of the study.

A patient may only be enrolled in one research study for which the IRB has required a flag advisory in the patient's electronic medical records. The IRB Chair must approve any exceptions in advance.

B. Criteria for Requiring Review More Often than Annually

(38 CFR 16.103(b)(4)(ii))

The IRB may determine that a protocol should be reviewed more frequently than annually. This may be determined at any time for any reason, including level of risk, nature of adverse events, and study population.

The IRB may consider the following factors in determining the criteria for which studies require more frequent review and what the timeframes generally will be:

1. Probability and magnitude (degree or risk) of anticipated risks to subjects.
2. Likely medical condition of the proposed subjects.
3. Overall qualifications of the principal investigator and other members of the research team.

4. Specific experience of the principal investigator and other members of the research team in conducting similar research.
5. Nature and frequency of adverse events observed in similar research at this and other facilities.
6. Vulnerability of the population being studied
7. Other factors that the IRB deems relevant.

In specifying an approval period of less than 1 year, the IRB may define the period with either a time interval or a maximum number of subjects, i.e., after 3 months or after three subjects. Examples of time intervals for IRB approval periods include 3, 6, 9, or 12 months. The IRB documents in the minutes the determination of risk level for a research project and approval period.

C. Independent Verification from Sources Other than the Investigator that No Material Changes Have Occurred Since the Previous IRB Review

(M-3, Part 1, Ch. 9.09 (c)(2))

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB verify independently, utilizing sources other than the investigator that no material changes occur during the IRB-designated approval period. Independent verification from sources other than the investigator may be necessary at times, for example, in cooperative studies, or other multi-center research.

The IRB shall consider the following factors in determining which studies require such independent verification:

1. Probability and magnitude of anticipated risks to subjects.
2. Likely medical condition of the proposed subjects.
3. Probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.
4. Prior experience with the principal investigator and research team.
5. Other factors that the IRB deems relevant.

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review, review of amendments and/or adverse events.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken.

D. Advertisements

The IRB must approve any and all advertisements prior to posting and/or distribution for studies that

are conducted under the purview of the PVAMC IRB. This information should be submitted to the IRB with the initial application or as an addendum to the protocol. The IRB reviews the material to assure that the material is accurate and is not coercive or unduly optimistic, creating undue influence to the subject to participate.

Any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included:

1. The name and address of the clinical investigator and/or research facility.
2. The condition being studied and/or the purpose of the research.
3. In summary form, the criteria that will be used to determine eligibility for the study.
4. The time or other commitment required of the subjects.
5. The location of the research and the person or office to contact for further information.
6. A clear statement that this is research and not treatment.
7. A brief list of potential benefits (e.g. no cost of health exam).

E. Recruitment Incentives

The IRB must approve any and all recruitment incentives to investigators, physicians, and other health care providers for identifying and/or enrolling subjects for studies that are conducted under the purview of the PVAMC IRB. The Principal Investigator must disclose this information on the IRQ, when a study is initially reviewed by the IRB. The IRB reviews the recruitment incentives to assure that the incentive is not coercive or unduly optimistic, creating undue influence for the researchers to recruit subjects into a study overall or by a certain date. Recruitment incentives will be reviewed according to the HRPP Policy & Procedure No. 5.

Recruitment Incentives to the investigator from a sponsor may not create undue influence to recruit patients for a study and must be reasonable in relation to the work being performed.

F. Payment to Research Subjects

(M-3, Part 1, Chapter 9.13, VHA Handbook 1200.5, 12)

The IRB reviews any financial or other form of payment to research subjects at the time of the initial application to assure that the amount is not coercive given the nature of the research or creates undue influence on the subject to participate. The information is provided in the IRQ, and additional information may be required on an as needed basis.

Payments may not be provided to subjects on a schedule that results in coercion or undue influence on the subject's decision to continue participation. For example, payment may not be withheld as a condition of the subject completing the research. If the subject withdraws early, payment must be prorated to reflect the time and inconvenience of the subject's participation up to that point. The schedule, amount and conditions of payment must be stated in the informed consent form.

VA policy prohibits paying subjects to participate in research when the research is an integral part of a subject's medical care and when it makes no special demands on the subject beyond those of medical care.

However, payment may be permitted, with prior approval of the IRB, in the following circumstances:

1. **No direct subject benefit.** When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated, non-VA institutions is to pay patients in this situation.
2. **Others being paid.** In multi-institution studies, where patients at a collaborating non-VA institution are to be paid for the same participation in the same study at the same proposed rate, the IRB may find that payment is appropriate.
3. **Comparable situations.** In other comparable situations in which, in the opinion of the IRB, payment of patient volunteers is appropriate.
4. **Transportation Expenses.** When transportation expenses are incurred by the subject that would not be incurred in the normal course of receiving treatment and which are reimbursed by another mechanism.

Investigators who wish to pay research subjects must indicate in their research project application the justification for such payment which may include consideration of the criteria listed above as well as:

1. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject;
2. State the terms of the subject participation agreement and the amount of payment in the informed consent form; and
3. Substantiate that subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure on the veteran patient to volunteer for the research study.

The IRB shall review all proposals involving the payment of subjects (in excess of reimbursement for travel) in the light of these guidelines. The Research Service office must ensure that such payments to subjects are made from appropriate funds.

G. Compensation for Injury

(38CFR16.116 (a)(6), 17.85)

Information on compensation for injury must be included in all informed consent forms for studies involving more than minimal risk, with contact names and telephone numbers, per the requirements of the text of the informed consent form.

VA medical facilities shall provide necessary medical treatment to a research subject injured as a result of participation in a research project approved by a VA Research & Development Committee and conducted under the supervision of one or more VA employees.

However, this requirement does not apply to (1) treatment for injuries due to non-compliance by a subject with study procedures; or (2) research conducted for the VA under a contract with an individual or a non-VA institution.

For additional information, regarding exceptions to this information, please see 38CFR17.85.

H. Certificates of Confidentiality

Where research involves the collection of highly sensitive information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes. This is rare in VA, however, in such situations the IRB may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC).

For studies not funded by DHHS, if there is an Investigational New Drug Application (IND) or an Investigational Drug Exemption (IDE), the sponsor can request a CoC from the FDA. The CoC was developed to protect against the involuntary release of sensitive information about individual subjects for use in federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings.

The IRB may determine that an investigator should request a certificate of confidentiality from the National Institute of Health (NIH) in cases when the information gathered for the research could be held against the research participant in a court of law. An investigator applies for a certificate of confidentiality through the NIH. The NIH will review the application and make a determination as to whether or not a CoC may be granted for the specific research project.

According to the NIH, if an investigator has submitted a CoC application to the NIH, recruitment of research subjects may begin prior to receiving a final determination from the NIH. If the NIH grants a CoC for the study, the CoC will apply retroactively to those research subjects enrolled.

The CoC does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities of child abuse or of a communicable disease. In addition, the CoC does not protect against the release of information to VA, DHHS or FDA for audit purposes. Consequently, the IRB may require that these conditions for release be stated clearly and explicitly in the informed consent document.

Additional information, regarding CoCs, including the application information necessary for applying for a Certificates of Confidentiality may be obtained on the NIH website at:

<http://grants1.nih.gov/grants/policy/coc/index.htm>.

I. Compliance with All Applicable State and Local Laws

The IRB follows and must adhere to all applicable state and local laws in the states of Oregon and Washington. Included in Appendix G is a reference to the applicable state statutes. The Research Service reviews Oregon and Washington state statutes annually to monitor changes in state statutes that relate to research.

All consent forms must be consistent with applicable state and local laws.

J. IRB Considerations About Ethical Study Design

The IRB takes into consideration the study design to assure that research ethics are being followed. This includes careful consideration of issues such as protection of privacy and confidentiality in epidemiological research, genetic research, and family research. Even studies, which, by their epidemiological nature may not require an informed consent form, are carefully evaluated to assure that only the information needed is being gathered, that the confidentiality of the information is carefully protected, and that the risk to the patient remains minimal.

K. IRB Considerations of Conflict of Interest

Please see HRPP, Policy & Procedure No. 5, "Conflict of Interest in Human Research," regarding IRB considerations of conflict of interest. This policy may be found in Appendix M. The conflict of interest policy applies to all full-time and part-time employees, members of governing panel or board and paid or unpaid consultants participating in human subjects research approved by the PVAMC IRB.

L. Principal Investigator Expertise

Studies which go beyond the individual expertise of the principal investigator into other medical generalist or specialty areas, may require that the principal investigator make certain that s/he has identified a qualified co-investigator or collaborator who will be in charge of patient safety. Such patient safety issues here include: making certain that abnormal laboratory/study results are reviewed in a timely fashion, patients are contacted about abnormal laboratory/study results in a timely fashion, and the abnormal laboratory/study results that could result in any patient injury are acted upon in an expedited manner. This co-investigator and collaborator will usually be involved in developing the scientific protocol section involving his or her area of expertise and training to assure optimal patient safety of follow-up of abnormal laboratory/study results. The co-investigator and collaborator will also be responsible with making all relevant communication to the patient's primary care provider about any new abnormalities of a moderate or severe nature and recording the same abnormalities in the patient's electronic medical record.

M. Credentialing and Education Verification for New Human Subjects Research Projects

The RACC will monitor new human subjects research projects as the Research Service office receives them. Individuals involved in a study approved by the VA IRB must complete the education and credentialing requirements consistent with HRPP Policies & Procedures Nos. 4 and 10. This is consistent with the 2003 Stand Down Requirements.

N. Participation of Non-Veterans as Research Subjects

(VHA Handbook 1200.5 , 16)

According to VHA Handbook 1200.5, non-veterans may be entered into VA approved research studies only when there are insufficient veterans available to complete the study in accordance with 38 CFR 17.45 and 38 CFR 17.92.

All the regulations pertaining to the participation of veterans as research subjects including requirements for indemnification in case of research-related injury pertain to non-veteran subjects enrolled in VA-approved research.

If an investigator would like to recruit non-veterans in a research project approved by the PVAMC IRB and conducted at the PVAMC, this will be considered by the IRB. The Principal Investigator should submit a request in writing to the IRB.

O. Ionizing Radiation

All studies involving Radiological devices or procedures are reviewed by the Radiation Safety Officer (RSO), who is a member of one IRB. Studies from the other IRB, which include a radiation component are also sent to the RSO for review. The RSO reviews the science of the radiation dose absorbed and performs an additional risk assessment particular to the use of radiation and assures that the use of radioactivity and the conduct of procedures are appropriate.

In the research plan, the investigator must clearly indicate on the IRQ, whether the research project involves any x-ray or radioactive materials. The PI must indicate the procedures, frequency and purpose. The PI must also determine if the procedures are those which the patient would receive even if they were not enrolled in the study, i.e. which procedures are standard of care.

In reviewing the study, the RSO will determine whether the planned exposure is within the allowable limit and whether or not the informed consent form adequately reflects the risks to subjects. The RSO will utilize the following guidelines when evaluating overall risk and the risk-benefit ratio:

1. Radiation exposure being done for the standard of care and uses routine procedures: The IRB may request review or consultation by the Radiation Safety Officer. The informed consent form will frequently make only general mention of the exposure.
2. Radiation exposure exceeds the standard of care, using routine procedures, and offers the prospect of direct benefit to the subject: The informed consent form must differentiate which procedures are being done for standard of care and which are being done solely for research. The informed consent form must state that the total dose exceeds standard care, and what risks may occur versus standard care. When radiation exposure is research-related, the informed consent form should clearly describe in lay language the quantity, significance, and risk, if any, of the radiation absorbed dose. The informed consent form must include the boilerplate information in the VA Informed Consent Template.
3. Radiation exposure exceeds the standard of care, using routine procedures, and offers no prospect of direct benefit to the subject: When radiation exposure is research-related, the informed consent form should clearly describe in lay language the quantity, significance, and risk, if any, of the radiation absorbed dose. The informed consent form must include the boilerplate information in the VA Informed Consent Template.

RR 605

Review of Research Involving Potentially Vulnerable Subject Groups (VHA Handbook 1200.5, Appendix D)

A. Vulnerable Populations

Vulnerable populations as listed in the Federal regulations include:

1. Pregnant women and fetuses;
2. Prisoners;
3. Mentally disabled and those with impaired decision-making capacity;
4. Children; and
5. Economically and educationally disadvantaged persons.

B. Pregnant Women and Fetuses as Vulnerable Populations

The Department of Health and Human Services (DHHS) regulations at 45 CFR Part 46, Subpart B detail special protections for research involving pregnant women, fetuses, and human in vitro fertilization. Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent.

Unilateral exclusion of non-pregnant women of reproductive potential from research is not permitted by the IRB. However, given compelling scientific justification this option may be considered by the IRB. Where such justification exists, it may also be appropriate to exclude men of reproductive potential.

Per VHA Handbook 1200.5, research in which the subject is a fetus, in-utero or ex-utero (including human fetal tissue) must not be conducted by VA investigators while on official duty, or at VA facilities, or at approved off-site facilities.

Per VHA Handbook 1200.5, research related to in vitro fertilization must not be conducted by VA investigators while on official duty, or at VA facilities, or at approved off-site facilities.

For research involving the participation of pregnant women as research subjects, the IRB must:

1. Determine that the proposed research meets the requirements outlined in Section VI, RR, 605, F;
2. Determine that adequate provision has been made to monitor the risks to the subject and the fetus.

3. Determine that adequate consideration has been given to the manner in which potential subjects are going to be selected, and that adequate provision has been made to monitor the actual informed consent process such as:

- (a) Overseeing the actual process by which individual consents required by this policy are secured either by approving enrollment of each individual into the activity, or by verifying, perhaps through sampling, that approved procedures for enrollment of individuals into the activity are being followed, and
- (b) Monitoring the progress of the activity and intervening, as necessary, through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen.

NOTE: These determinations should be documented in the IRB minutes.

4. General limitations

- (a) Activities related to pregnant women must not be undertaken unless:
 - (1) Except if appropriate studies on animals and non-pregnant individuals have been completed, and data for assessing potential risks to pregnant women and fetuses is provided.
 - (2) The purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal, and, in all cases, is the least possible risk for achieving the objectives of the activity.
 - (3) Individuals engaged in the activity will have no part in:
 - (i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy; or
 - (ii) Determining the viability of the fetus at the termination of the pregnancy.
 - (iii) Introducing any procedural changes, for research purposes, into the procedures for terminating the pregnancy.
- (b) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of research activity
- (c) No pregnant woman may be involved as a subject in a research activity unless:
 - (1) The purpose of the activity is to meet the health needs of the mother, and the fetus will be placed at risk only to the minimum extent necessary to meet such needs; or
 - (2) The risk to the fetus is minimal.

- (3) The mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if:

- (i) The purpose of the activity is to meet the health needs of the mother,
- (ii) His identity or whereabouts cannot reasonably be ascertained,
- (iii) He is not reasonably available, or
- (iv) The pregnancy resulted from rape.

C. Prisoners as a Vulnerable Population in Research

The PVAMC does not conduct research involving prisoners.

Prisoners are considered a vulnerable population because both their incarceration and the constraints imposed on them during their incarceration may render them unable to make a truly informed and voluntary decision regarding whether or not to participate as subjects in research. Therefore, research involving prisoners must not be conducted by VA investigators while on official duty, or at VA-approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer. If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to prisoners as research subjects (see 45 CFR Part 46, Subpart C 46.301 – 46.306, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects). **NOTE:** Requirements for requesting a waiver may be obtained through the Research Office by contacting the Office of Research and Development at VA Central Office or by accessing the VA research web site at <http://www.va.gov/resdev>.

D. Minors (Children) as a Vulnerable Population in Research

The PVAMC does not conduct research, involving minors (children).

The VA is authorized to care for veterans and to conduct research that supports the mission of VHA and that enhances the quality of health care delivery to veterans. Therefore, research involving children must not be conducted by VA investigators while on official duty or at VA or approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer. If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to children as research subjects (see 45 CFR Part 46, Subpart D 46.401 – 46.409, Additional Protections for Children Involved as Subjects in Research). **NOTE:** For requirements for requesting a waiver, the Research Office will contact VA Central Office.

E. Mentally Disabled or Those Persons With Impaired Decision Making Capacity as a Vulnerable Population in Research

Policies regarding research involving mentally disabled or those persons with impaired decision making capacity are described in Section VI, RR, 606.

F. Elements to Consider in Reviewing Research Involving Vulnerable Subjects

Department of Veterans Affairs (VA) regulations at 38 CFR 16.111 (b) and Food and Drug Administration (FDA) regulations require the IRB to give special consideration to protecting the

welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

The IRB is required to consider the scientific and ethical reasons for including vulnerable populations in research. The IRB is also required to have adequate representation on the IRB to consider specific kinds of research involving these vulnerable populations in a satisfactory manner.

The IRB must pay special attention to specific elements of the research plan when reviewing research involving vulnerable subjects. These specific elements may include the following:

1. Strategic issues such as inclusion and exclusion criteria for selecting and recruiting participants; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.
2. The IRB carefully considers group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable subjects.
3. Investigators are not permitted to over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available "captive" population.
4. The IRB is knowledgeable about applicable state or local laws that bear on the decision-making abilities of potentially vulnerable populations. Some of the issues addressed in Oregon and Washington State statutes are related to competency to consent, legally authorized representatives, and the age of majority for consent.
5. Just as in providing medical care, research studies that plan to involve any potentially vulnerable populations must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable subjects, the IRB shall look to see that such procedures are a part of the research plan. In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples may include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a subject advocate, interpreter for hearing-impaired subjects, translation of informed consent forms into languages the subjects understand, and reading the consent form to subjects slowly and ensuring their understanding paragraph by paragraph.
6. The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB requires that the investigator submit each signed informed consent form to the IRB. The IRB may also require that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

RR 606**Review of Research on Human Subjects
Likely to Need Surrogate Consent
(VHA Handbook 1200.5, 11)**

In all cases, the IRB takes special care to consider issues such as the selection of subjects, privacy and confidentiality, coercion and undue influence, and risk-benefit analysis. Decisions should be made with the utmost deference to the ethical principles underlying human subjects research as set forth in the Belmont Report. Capacity should be evaluated on an individual basis to avoid incorrect assumptions as to an individual's ability to make decisions. In cases where research involving cognitively impaired individuals is approved, the IRB may require additional safeguards (e.g., involvement of subject advocates, independent monitoring, formal capacity assessment, waiting periods) as part of the research plan to protect participants.

Research involving subjects who may have impaired decision-making capacity warrants special attention. Research involving these populations may present greater than minimal risk; may not offer direct medical benefit to the subject; and may include a research design that calls for washout, placebo, or symptom provocation. In addition, these populations may be vulnerable to coercion. Such subjects must be protected from exploitation and harm while allowing the conduct of essential research on problems that are unique to this population.

A. IRB composition

1. The IRB membership must include at least one member who is an expert in the area of the research. Consideration may be given to adding another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population.
2. The IRB may utilize ad hoc members as necessary to ensure appropriate expertise.

B. Conditions of Approval

Research involving persons with impaired decision-making capability may only be approved when the following conditions apply:

1. **Only incompetent persons are suitable**
Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.
2. **Favorable Risk/Benefit Ratio.** The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of

injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.

3. **Well-Informed Representatives.** Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Health care agents (appointed under Durable Power of Attorney for Health Care (DPAHC)) and next-of-kin, or guardians, must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

If the IRB finds that these criteria have been met, incompetent subjects may be enrolled. Such approval may be sought with the initial application, may be requested later as a study modification, or approval may be sought as needed on a case-by-case basis.

C. **IRB Documentation**

The IRB must make a determination in writing of each of the criteria listed in Section VI, RR, 606, B. If these criteria are met, the IRB may approve the inclusion of incompetent subjects or subjects with impaired decision-making capacity in research projects on the basis of informed consent from authorized representatives as defined below in Section VI, RR, 606, E.

D. **Fluctuating Capacity to Consent**

Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary. Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

A person who is incompetent or has been determined to lack capacity to consent to participate in a research study should be informed about the trial to the extent compatible with the subject's understanding and, if possible, the subject should give their assent to participate, sign and date the written informed consent or a separate assent form. If the person objects to participating, this objection should be heeded.

E. **Legally Authorized Representative**

In instances where the subject may not be able to give consent for him/herself, the subject's ability to consent must be first be assessed. If it has been verified that the potential research participant is unable to give informed consent for him/herself, his/her legally authorized representative may consent on behalf of him/her to participate in the procedure(s). Consistent with VA policy, state/local law, a legally authorized representative is defined as an individual, or judicial or other body, authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research in the following descending order of priority:

- a. A "legally authorized representative" includes not only persons appointed as healthcare agents under Durable Powers of Attorney for Health Care (DPAHC)
- b. Court appointed guardians of the person
- c. Spouse

- d. A majority of the adult children (18 years of age or older) who can be so located
- e. Parent
- f. A majority of the adult siblings (18 years of age or older) who can be so located

Note: the preceding list contains the only surrogate entities who are allowed to provide consent for research purposes. Refusal to consent by a person who is a higher priority surrogate shall not be superseded by the consent of a person who is a lower priority surrogate. Additionally, if there are two or more individuals in the same class and the decision is not unanimous among all available members of the class, then no person under this section may provide informed consent. Surrogates may not receive financial compensation for providing the consent.

A person who is incompetent or has been determined to lack capacity to consent to participate in a research study should be informed about the trial to the extent compatible with the subject's understanding and, if possible, the subject should give their assent to participate, sign and date the written informed consent or a separate assent form. If the person objects to participating, this objection should be heeded.

F. Inclusion of subjects who may lack capacity for informed consent:

The decisional capacity of a potential research subject should be evaluated when there are reasons to believe that the subject may not be capable of making voluntary and informed decisions about research participation.

The investigator and research staff must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent.

For research protocols that involve subjects with mental disorders that may affect decision-making capacity, the IRB may determine that capacity assessments are necessary, unless the investigator can justify why such assessments would be unnecessary for a particular group.

For research that poses greater than minimal risk, the IRB may require investigators to use independent and qualified professionals to assess whether potential subjects have the capacity to give voluntary, informed consent. Even in research involving only minimal risk, the IRB may require that the study include a capacity assessment if there are reasons to believe that potential subjects' capacity may be impaired. It is not necessary to require a formal capacity assessment by an independent professional for all potential research subjects with mental disorders.

For research protocols involving subjects who have fluctuating or limited decision making capacity the IRB may ensure that investigators establish and maintain ongoing communication with involved caregivers. Periodic re-consent should be considered in some cases. Third party consent monitors may be used during the recruitment and consenting process, or waiting periods may be required to allow more time for the subject to consider the information that has been presented.

It is often possible for investigators and others to enable persons with some decisional impairments to make voluntary and informed decisions to consent or refuse participation in research. Potential measures include repetitive teaching, group sessions, audiovisual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess subject understanding, videotaping or audio-taping of consent interviews, second opinions, use of independent consent

observers, interpreter for hearing-impaired subjects, allowing a waiting period before enrollment, or involvement of a trusted family member or friend in the disclosure and decision making process.

G. Determining capacity to consent:

Decisional capacity in the research context has been interpreted by the American Psychiatric Association as requiring: (1) ability to evidence a choice; (2) ability to understand relevant information; (3) ability to appreciate the situation and its likely consequences; and (4) ability to manipulate information rationally. A range of professionals and methods may be utilized to assess capacity. In general the consent assessor should be a researcher or consultant familiar with dementias and qualified to assess and monitor capacity and consent in such subjects on an ongoing basis. The IRB will consider the qualifications of the proposed individual(s) and whether he or she is sufficiently independent of the research team and/or institution.

The majority of studies conducted at the PVAMC only allow enrolling subjects who have the capacity to consent. For studies that have been approved for enrolling vulnerable populations who may lack capacity to consent, there must be someone who is able to assess capacity of each potential subject to consent. If the PI makes the initial judgment that the potential subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time, then this must be confirmed in consultation with the chief of service or Chief of Staff. Additionally, if the reason for lack of capacity is because of mental illness then a psychiatrist or licensed psychologist must confirm this judgment and document in the individual's medical record in a signed and dated progress note.

A person who has been determined to lack capacity to consent to participate in a research study must be notified of that determination before permission may be sought from his or her legally authorized representative to enroll that person in the study. If permission is given to enroll such a person in the study, the potential subject must then be notified. Should the person object to participating, this objection should be heeded.

A surrogate must be fully informed of the study and have sufficient opportunity to consider what the wishes of the potential subject would be and whether or not to consent on behalf of the subject. The surrogate must receive all of the information a regular enrollee would receive in language that is understandable to the surrogate. Surrogate consent will be accepted in the order identified in the SOP and consistent with Oregon and Washington state law. If the potential subject indicates that s/he does not wish to participate then the surrogate consent cannot be honored.

When surrogate consent is used, it must be documented in writing by the investigator that the surrogate is named; made aware of their responsibility; that they have been informed about risks/benefits of the study and are aware that the subject had consented to participate; that they are aware of their rights to withdraw and to contact the PI or Research Service for questions/problems; that the subject, if possible, has given their assent to participation in the study; that the surrogate will be informed of future information that is needed to be an informed participant. Progress notes during the period of surrogate consent should note that subject himself/herself demonstrates no dissent from participation in the study.

H. IRB Procedures

The IRB will document that all of the criteria listed in Section VI, RR, 606, B, above have been met. If these criteria are met, the IRB may approve the inclusion of incompetent subjects or subjects with impaired decision making capacity in research projects. In considering such studies, it is

recommended that the IRB include at least one member who is familiar with the population to be recruited. The IRB is encouraged to utilize ad hoc members as necessary to assure appropriate expertise. The protocol should describe who will conduct the assessment, the method by which prospective subjects' decisional capacity will be evaluated, and the criteria for identifying incapable subjects. Less formal procedures to assess potential subjects' capacity may be permitted if a formal assessment is not feasible. Less formal procedures could include the ways professionals often make judgments about capacity in routine interactions.

The IRB has the authority to require review of the study at earlier intervals, to impose conditions on the use of surrogate consent or prohibit its use entirely, or to require additional reporting by the investigator.

EX 701**Expedited Review of Research**
(38 CFR 16.110)

The IRB Chairs will make a determination on whether or not a protocol may be reviewed using expedited procedures. The individual(s) making this determination cannot be involved in the proposed research. The determination on whether or not a protocol may be reviewed using expedited procedures is based on either or both of the following:

- (1) The research constitutes a minor change in previously approved research during the period of 1 year or less for which approval is authorized; or
- (2) The research is not greater than minimal risk and falls within the categories on the November 9, 1998, DHHS-FDA list of research eligible for expedited IRB review published in the Federal Register, 63 FR 60364-60367 (Section VII, EX, 703).

The Chairs may review the expedited review request and research project or the Chairs may designate a qualified designee to complete the review of the request and research project. The qualified designee to review the request and research project must be a voting member of the IRB and have qualifications, experience and knowledge in the content of the protocol to be reviewed, as well as be knowledgeable of the requirements to approve research expeditiously. The reviewer may exercise the authority of the IRB, but may not disapprove the research. If the IRB Chair or qualified designee does not approve the research through expedited procedures, then the research project will be reviewed by the convened IRB. The research may only be disapproved after non-expedited review by the convened IRB.

The fully convened IRB will be notified of all research approved under expedited procedures in the IRB meeting agenda and minutes. A copy of the expedited request and approval, or appropriate items, will be included in the IRB agenda packets for review by the convened IRB. All correspondence resulting from an expedited review will note such and be filed with the Research Services research project file kept in the appropriate Research Service space. Documentation for expedited reviews maintained in IRB records shall include the category and circumstances that justify using expedited procedures.

EX 702**Expedited Review of Minor Changes in Previously Approved Research
(38 CFR 16.110(b)(2))**

VA regulations at 38 CFR 16.110, the Common Rule, and FDA regulations permit the IRB Chair or his/her qualified designee(s) to review research through an expedited procedure if minor changes are in previously approved research during the period (of one year or less) for which the approval is authorized. The expedited review and reviewer requirements are such as stated in Section VII, EX, 701, above. The individuals making this determination cannot be involved in the proposed research.

A **minor change** is one which, in the judgment of the IRB Chairperson or qualified designee, makes no substantial alteration in (1) the level of risks to subjects; (2) the research design or methodology; (3) the number of subjects enrolled in the research; (4) the qualifications of the research team; (5) the facilities available to support safe conduct of the research; or (6) any other factor which would warrant review of the proposed changes by the convened IRB.

Investigators must report to the IRB any proposed changes in IRB-approved research, including proposed changes in informed consent documents. The investigator may request an expedited review of minor changes in previously approved research. However, no changes may be initiated without prior approval of the IRB, except where necessary to eliminate apparent immediate hazards to subjects.

The fully convened IRB will be notified of all minor changes in research approved under expedited procedures in the IRB meeting agenda and minutes. A copy of the expedited request and approval, or appropriate items, will be included in the IRB agenda packets for review by the convened IRB. All correspondence resulting from an expedited review will note such and be filed with the Research Service's research project file kept in the appropriate Research Service space. Documentation for expedited reviews maintained in IRB records shall include the category and circumstances that justify using expedited procedures.

EX 703**Expedited Initial and Continuing Review: Permitted Categories****A. Applicability of Expedited Review**

Expedited procedures are used for initial and continuing review of research that is no greater than minimal risk **and** falls within the categories published in the November 9, 1998, Federal Register 63 FR 60364-60367. The IRB uses the following criteria for determining whether or not the risks to the subjects are minimal: under VA regulations at 38 CFR 16.102 (i), “minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” The categories for research projects eligible for expedited initial and continuing review are stated below. Even though a proposed research project may fall into the following categories, expedited review will be considered but is not guaranteed.

Applicability:

- (1) Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
- (2) The categories in this list apply regardless of the age of subjects, except as noted.
- (3) The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subject’s financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- (4) The expedited review procedure may not be used for classified research involving human subjects.
- (5) The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

B. Permitted Categories of Research

All of the below categories pertain to initial and continuing review of research projects. These

categories include:

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met:

(a) Research on drugs for which an investigational new drug application (21 CFR 312) is not required. (*Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.*)

(b) Research on medical devices for which (a) an investigational device exemption application (21 CFR 812) is not required; or (b) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Section of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

- (5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (*Note: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects at 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.*)
- (6) Collection of data from voice, video, digital, or image recordings made for research purposes.
- (7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (*Note: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. 45 CFR 46.102(b)(2) and (b)(3). This listing refers only to research that is not exempt.*)

For **continuing reviews**, expedited reviews will only be considered in the following circumstances:

- (8) Continuing review of research previously approved by the convened IRB as follows:
 - (a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
 - (b) Where no subjects have been enrolled and no additional risks have been identified; or
 - (c) Where the remaining research activities are limited to data analysis.
- (9) Continuing review of research, which is **not** conducted under an investigational new drug application or investigational device exemption and where the categories for initial review (1)-(7) and continuing review (8) do not apply, but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

IC 801

Informed Consent Requirements and Documentation

A. Purpose of the Informed Consent Documentation

One overarching requirement of research involving human subjects is that investigators must obtain the legally effective or the subject's legally authorized representative informed consent of prospective subjects **before** the subject can be entered into the study and before conducting any procedures required by the protocol, unless the informed consent requirements are waived by the IRB. Informed consent presumes two simultaneous concepts: informed decision-making and voluntary participation. Prospective subjects must be given sufficient information about the research and its risks and benefits to reach an **informed decision** as to whether they will **voluntarily participate**.

Informed consent is an ongoing process of information exchange between the prospective research participant and trained individual conducting the consent process, not simply a signed consent form. The informed consent session must take place with the subject or his/her legally authorized representative PRIOR to having any of the procedures conducted, unless the requirements of informed consent are waived by the IRB. The consenting process begins with the information given during subject recruitment, as well as oral instructions, the written informed consent form and any other materials approved by the IRB, the ability for the individual to ask questions, the signed written agreement by the subject or legal representative and if the subject has additional questions, concerns, or if the study presents new data necessary to present to the subject as the study progresses. If a potential subject or legally authorized individual seems hesitant about participating in a study or feels they should discuss participation with any family members, the investigator or his/her representative must allow the patient ample time to discuss the study with his/her family and make his/her decision. This may require having the patient contact the investigator or representative at a later time to agree to participate in the study. Throughout the study, the investigator and his/her representatives should encourage the patient to ask questions that he/she may have throughout the procedures or study visit(s).

B. Circumstances of Informed Consent Requirements

(38 CFR 16.111(a)(4) and 38 CFR 16.116)

To approve research, the IRB must determine that legally effective informed consent shall be sought from each prospective subject or the subject's legally authorized representative (see 38 CFR 16.116), unless informed consent requirements can be waived or altered under VA regulations. All informed consent forms and any such waiver must be consistent with applicable Washington and Oregon state law regarding content and participation in research.

Informed consent may only be sought under circumstances that provide the subject (or the legally authorized representative) with sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence (38CFR16.116). These circumstances include:

1. Assessing the prospective research participant's capacity to consent to the research protocol, prior to consenting the individual, to ensure that s/he is able to understand the study procedures and all risks and benefits in order to make an informed decision. The IRB may determine that for a high-risk study, procedures should be put in place to assess the research participant's capacity to consent.

2. Presenting and ensuring the informed consent information is presented in a language that is understandable to the subject (or the subject's legally authorized representative).
3. Excluding any exculpatory language from the informed consent process
 - (a) through which the subject is made to waive, or appear to waive, any of the subject's legal rights; or
 - (b) through which the investigator, the sponsor, the PVAMC, or the PVAMC's employees or agents are released from liability for negligence.
4. Obtaining informed consent prior to initiation of any clinical screening procedures that are performed solely for the purposes of determining eligibility for research.
5. Providing the prospective subject or the legally authorized representative sufficient opportunity to consider whether or not to participate.
6. Ensuring that subjects give consent without coercion or undue influence.

C. Documentation of Informed Consent

(38 CFR 16.117)

To approve research, the IRB must determine that informed consent shall be appropriately documented, on VA Form 10-1086, properly executed with appropriate signatures of the subject or legally authorized representative, witness, and person obtaining consent, date, time, and social security number as required by the IRB, unless documentation can be waived by the IRB under VA regulations, the Common Rule, or FDA regulations. IRB approval of the wording of the consent must be documented through the use of a stamp on each page of the VA Form 10-1086 that indicates the date of the most recent IRB approval of the document. If the PI is not conducting the informed consent process, the PI must initial that s/he has reviewed the informed consent document and attest to the integrity of the informed consent process. The witness, except when informed consent is being obtained orally, is only witnessing the signature on the informed consent document and may not be involved in the research project at hand.

Informed consent must be obtained prior to entering a subject into a study and the conduct of any procedures required by the protocol, unless the informed consent requirement is waived by the IRB.

VA regulations at 38 CFR 16.117, the Common Rule, and FDA regulations provide two methods for documenting informed consent:

1. Written Informed Consent Document

Consent may be documented through use of a written consent document that embodies all of the required elements of informed consent (these elements are discussed in detail in Section VIII, IC, 801 N-P). The VA 10-1086 consent document form shall be used and must be signed by the subject (or the subject's legally authorized representative), and a copy must be given to the person signing the form. FDA regulations require that the signature be dated. This form may be read to the potential research participant or his/her legally authorized representative. The potential participant/legally authorized representative must be given adequate time to read the document and make a decision, regarding participation, prior to signing the informed consent document.

2. Short Form Written Informed Consent

Consent may also be documented through use of a “short form” written consent document, which states that the elements of informed consent have been presented orally to the subject (or the legally authorized representative) in a language understandable to the subject. The oral presentation must contain all of the information that is contained in the informed consent document. When this method is used the following is necessary:

- (a) The IRB must approve a written summary of what is to be presented orally and the “short form” written consent document;
- (b) There must be a witness to the oral presentation;
- (c) The witness must sign both the “short form” and the written summary presented to the subject or legally authorized representative;
- (d) Only the “short form” must be signed by the subject or the representative;
- (e) The person obtaining the informed consent must sign the written summary; and
- (f) A copy of the summary and the “short form” must be given to the subject or the representative.

PVAMC policy is that the original signed consent document must be forwarded to the Research Service within 72 hours of consenting the patient. The Research Service scans the consent form into the patient’s electronic medical record in the Computerized Patient Record System (CPRS). After the informed consent form is scanned into the patient’s electronic medical record, the original signed consent form will be forwarded to the Principal Investigator for inclusion in the Principal Investigator’s case history files. A copy must be given to the patient and the patient must initial the original signed consent form acknowledging receipt of a copy of the informed consent form. When applicable, a copy must also be forwarded to the Research Pharmacy, prior to dispensing any investigational drug.

It is the responsibility of the Research Service to assure that this is being done appropriately. Results of internal audits and recommendations for corrective action, if needed, will be reported to the IRB and R&D Committee for deliberation.

D. Individuals Authorized to Conduct the Informed Consent Process

The Principal Investigator is authorized to conduct the informed consent process. If the PI is not available to inform the prospective subject about all aspects of the research project (trial) or conduct the informed consent process, the PI may delegate these responsibilities to an individual or individuals who is/are properly trained to inform the prospective subject about all aspects of the research project and conduct the informed consent process.

The Principal Investigator is responsible for ensuring that the individuals s/he authorizes to inform the prospective subject about all aspects of the research project and conduct the informed consent process are knowledgeable of the research project and procedures as well as the informed consent process. The designee should be able to answer questions raised by the potential research participant or legally authorized representative. All authorized individuals must complete the education and credentialing

requirements consistent with HRPP Policies and Procedures Nos. 4 and 10.

If the PI does not conduct the informed consent process, he/she must initial the informed consent document confirming that he/she has reviewed the informed consent document and attests to the integrity of the informed consent process. The signature page containing this signature line may be found on the R&D Service website:

<http://www.va.gov/portlandrd/pages/support/award/form.htm>

E. Observation of the Informed Consent Process

(M-3, Part 1, Chapter 9.09 (f))

The IRB has the authority to observe the informed consent process of any research study, which is currently active. An IRB member or designee may observe a consent session as an impartial observer or conduct structured interviews of research participants.

In addition, informed consent documentation is reviewed and overseen through the following mechanisms: 1) the IRB or its designee, which may include the IRB Coordinators and/or staff, carefully review each signed informed consent form which is turned in for inclusion into the patient's CPRS record to assure that it was correctly completed and that all required signatures are in place and 2) the Quality & Performance Service may conduct audits of informed consent documentation.

F. Assessing a Potential Subject's Capacity to Consent

A subject's capacity to give consent should be evaluated on an individual basis to avoid incorrect assumptions as to the subject's ability to make decisions and to ensure that the subject is able to understand the study procedures and all risks and benefits involved so that the subject may make an informed decision prior to consenting the individual.

In cases where research involving cognitively impaired individuals is approved, the IRB may require additional safeguards (e.g., involvement of subject advocates, independent monitoring, formal capacity assessment, waiting periods) as part of the research plan to protect participants. The IRB will determine when a subject's capacity to consent is required. This is based on the potential subject population and risks to subjects

More information, regarding assessing a potential subject's capacity to consent, may be found in Section VI, RR, 606.

G. Surrogate Consent

Under appropriate conditions, investigators may obtain consent from the legally authorized representative of a subject (surrogate consent). More information, regarding surrogate consent, may be found in Section VI, RR, 606.

H. Legally Authorized Representative

Under appropriate conditions, investigators may obtain consent from the legally authorized representative of a subject (surrogate consent). More information, regarding surrogate consent, may be found in Section VI, RR, 606, E.

I. Witnesses of Informed Consent Process

The IRB requires that a witness, a person unassociated with the research project for which an individual is consenting, be present during the:

1. Signature of the written informed consent document. The witness does not need to witness

the entire informed consent process, only the signing of the document. The witness must also sign the written informed consent document.

2. Informed consent process when a “short form” written consent is being used. The witness must sign both the short form written consent document and the summary of the oral presentation given to the subject or the subject’s legally authorized representative.

Ideally, the witness could be a family member or friend of the research participant.

J. Informed Consent Reading Level and Language

(38 CFR 16.116)

VA regulations at 38 CFR 16.116, the Common Rule, and FDA regulations require that informed consent is at the appropriate reading level of the potential patient population and be obtained in a language that is understandable to the subject (or the subject’s legally authorized representative).

In cases where informed consent must be obtained from non-English speakers, the Principal Investigator is responsible for working with the IRB to determine that an effective and appropriate method is in place. This may include the use of a reliable, certified translator or a certified translation of the informed consent document.

K. Exculpatory Language

The IRB prohibits the informed consent, written or oral, from containing any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject’s legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

L. Waiver of Documentation of Consent

(21CFR56.109(c))

VA regulations at 38 CFR 16.117(c) permit an IRB to waive the requirement to obtain written documentation of informed consent. (**Note:** This provision can be used only for the waiver of documentation of consent, not for waiver or alteration of consent itself.)

To approve such a waiver, the IRB must find and document **either** of the following conditions:

- (1) The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. In this case, each subject may be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (The waiver provision is **not** applicable to FDA-regulated research).

OR

- (2) The research presents no more than minimal risk of harm to subjects and involves procedures or activities for which written consent is not normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the principal investigator to provide subjects with a written statement regarding the research. This policy is applicable to FDA-regulated research.

IRB minutes shall clearly reflect this waiver provision and the justification for its use. In addition, the IRB may also waive the Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements for an authorization for research purposes. In these cases, the IRB must additionally document the justification for its use. Please see HRPP Policy & Procedure, No.6, located in Appendix N.

M. Waiver or Alteration of Informed Consent Requirements: Minimal Risk Research

VA regulations at 38 CFR 16.116(d) permit the IRB to approve a consent procedure which does not include or which alters some or all of the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. To approve such a waiver or alteration, the IRB must find and document that:

- (1) The research involves no more than minimal risk to the subjects.
- (2) The waiver or alteration shall not adversely affect the rights and welfare of the subjects.
- (3) The research could not practically be carried out without the waiver or alteration.
- (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

These findings and their justifications shall be clearly documented in IRB minutes when the IRB exercises this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the IRB cannot approve such alterations or waivers for FDA-regulated research (21 CFR 50.20).

The waiver or alteration of informed consent requirements for FDA regulated articles is described in Section VIII, IC, 802, A.

In addition, the IRB may also waive the Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements for an authorization for research purposes. In these cases, the IRB must additionally document the justification for its use. Please see HRPP Policy & Procedure, No.6, located in Appendix N.

N. Required Elements of Informed Consent Forms

A written consent document embodies the elements of informed consent. To ensure an effective informed consent process, Department of Veterans Affairs (VA) regulations, the Common Rule, and Food and Drug Administration (FDA) regulations mandate the inclusion of the fundamental informed consent elements and the additional elements when appropriate. Depending on the nature of the research an investigator may request elimination of any of the elements.

In accordance with 21 CFR 50.25, 38 CFR 16.116, 45 CFR 46.116 and VA Handbook 1200.5, the following information will be provided to each subject:

1. **Name of the Study**
2. **The name of the Principal Investigator**

3. **A statement that the study involves research**
4. **An explanation of the purposes of the research**
5. **The expected duration of the subject's participation**
6. **A description of the procedures to be followed**
7. **Identification of any procedures which are experimental**
8. **Description of any reasonably foreseeable risks or discomforts to the subject**

Informed consent information must describe any reasonably foreseeable risks or discomforts associated with the research. Risks may include physical, psychological, social or economic risks.
9. **Reasonably expected benefits to subjects or others**

Informed consent information must describe any benefits to subjects or to others that may reasonably be expected from the research. However, care must be taken not to overstate the benefits and create an undue influence on subjects. Payment for subject's participation in a research project is not to be considered as a benefit of the research.
10. **Appropriate alternatives to participation**

Informed consent information must include a disclosure of any appropriate alternative procedures or courses of treatment that may be advantageous to the subject.
11. **Extent of privacy and confidentiality**

Informed consent information must describe the extent to which confidentiality of records identifying the subject will be maintained. Research often poses the risk of loss of confidentiality to subjects who participate. Many persons who would not otherwise have access to identifiable, private information about the subject may be involved in the research process. Consent information should describe any procedures that the research team will use to protect subjects' private records. In some research, loss of privacy may be the greatest risk of participation. For FDA regulated studies, consent forms must include that the FDA may inspect research records.

Research projects which will combine the HIPAA Authorization requirements into the informed consent form will require that 9 additional elements be added to the informed consent form. Please refer to the HRPP Policy and Procedure, No. 6, regarding the additional elements required if the HIPAA Authorization is included in the informed consent form.
12. **Compensation or treatment for injury**

Informed consent information for research involving more than minimal risk must include explanations regarding:

- (a) Whether any compensation is available and an explanation as to whether any medical treatments are available if injury occurs and if so, what they consist of or where further information may be obtained.
- (b) In accordance with Federal law, a statement that veteran-subjects shall receive medical care and treatment for injuries suffered as a result of participating in a VA research program and whether any medical treatments are available if injury occurs.

13. Contact information

Informed consent information must include details, including telephone numbers, about whom to contact for three specific situations:

- (a) For answers to questions about the research. The principal investigator and other members of the research team are appropriate contacts for this information.
- (b) For answers to questions about subjects' rights contact information. The Research Service is an appropriate contact for this information.
- (c) In the event of a research-related injury occurs to the subject. The VA Regional Counsel and the Investigators are all appropriate contacts for this information.

14. Voluntary participation statement

It is particularly important in the VA context for subjects and prospective subjects to understand and have complete confidence that failure to participate will not jeopardize their VA provided care. Informed consent information must contain statements of the following:

- (a) Participation in the research is voluntary.
- (b) Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subjects is entitled.

15. Payment for treatment

Informed consent information must include a statement that veteran-subjects shall not be required to pay for treatment received as a subject in a VA research program. Investigators should note, however, that certain veterans are subject to co-payments for medical care, pharmaceutical, and services provided by VA.

O. Additional Elements Where Appropriate

In accordance with 21 CFR 50.25, 38 CFR 16.116, 45 CFR 46.116 and VA Handbook 1200.5, the following information will be provided to each subject, when appropriate.

1. Unforeseeable risks to subjects, embryos, or fetuses

A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus if the subject is or may become pregnant) that are currently unforeseeable.

Explanation: Some research involves particular procedures or interventions that may result in unforeseeable risks to subjects, to the embryo, or the fetus (if the subject is or may become pregnant).

2. Investigator-initiated termination of participation

The informed consent information must specify the anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

Explanation:

There may be instances that would require investigators to terminate the participation of particular subjects (e.g., subject non-compliance with research, subject not benefiting from research).

3. Additional costs

Any additional costs to the subject that may result from participation in the research, with consideration of Federal laws concerning veterans' eligibility for medical care and treatment.

4. Early withdrawal/procedures for termination

The consequences of a subject's decision to withdraw from the research and the procedures for orderly termination of participation by the subject.

Explanation:

Subjects have the right to withdraw from the research. However, some studies involve medications or procedures that would be dangerous for subjects to discontinue abruptly. For studies of this nature, the informed consent information must provide subjects with knowledge of the consequences affecting a decision to withdraw. In addition, if there are procedures regarding how to withdraw safely from the research, these must also be described. It is not appropriate for research staff to administer any additional research-oriented questionnaires or interventions that do not affect the safety of subjects who have decided to withdraw.

5. Significant new findings

A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

Explanation:

During the course of research, significant new knowledge or findings about the medication or test article and/or the condition under study may develop. Since the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the informed consent information must detail the procedures for contacting subjects regarding this new information and for affirming their continued participation.

6. Approximate number of subjects

The approximate number of subjects involved in the study.

7. FDA regulated studies.

If the research involves an FDA-regulated test article, the FDA requires a statement that the FDA may choose to inspect research records that includes the subject's individual medical records.

8. Payment for participation.

As appropriate, a statement regarding:

- (a) information concerning the amount of payment to subjects and
- (b) information concerning the schedule of payments to subjects.

Explanation:

The informed consent information should include a clear statement describing any payment the subject is to receive for participation, the required conditions for payment, and the payment schedule. Since VA regulations at 38 CFR 16.116(a)(8), the Common Rule, and FDA regulations all state that subjects may withdraw from research at any time without penalty of loss of benefits to which they are otherwise entitled, completing the research may not be made a condition of payment. For this reason the informed consent information should be a description of how payment will be prorated and calculated for subjects who withdraw early.

P. Human Biological Specimen Consent Form Requirements

(Memorandum of 03/28/2001, VHA Directive 2000-043, M-3, Chapter 9, Appendix 9C)

If the investigators believe that human biological specimens obtained as part of a research study could be part of, or lead to the development of a commercially valuable product, or if the specimens are to be retained after the end of the study, VA policy and VHA regulations must be followed.

1. If the researchers believe that the bodily fluids, substances or tissues of a research subject could be part of or lead to the development of a commercially valuable product, the following verbatim statement is required. "By consenting to participate, I authorize the use of my bodily fluids, substances, or tissues."
2. Statement of whether or not the specimen will be used for future research and allow the choice of how the specimen will be used (any research, research by the PI, or other researchers, genetic analysis, research related to specific area, etc.).
3. Whether or not the research results of future use of the specimen will be conveyed to the subject.
4. Whether or not the subject will be re-contacted after the original study is completed.

5. If the subject requests, the specimen and all links to the clinical data will be destroyed.

Q. Progress Notes

(VHA Handbook 1200.5, Appendix C)

A progress note documenting the informed consent process must be placed in the subject's CPRS medical record. The Principal Investigator is responsible for ensuring that the progress notes are assigned appropriately for each individual subject.

1. At a minimum, the progress note must include:
 - (a) The name of the study,
 - (b) The person obtaining the subject's consent,
 - (c) A statement that the subject or the subject's legally-authorized representative was capable of understanding the consent process,
 - (d) A statement that the study was explained to the subject, and
 - (e) A statement that the subject was given the opportunity to ask questions.
2. An entry must also be placed in the progress note when the human subject is actually entered into the study and when the human subject's participation is terminated.
3. Consent and entry notes may be combined when both occur at the same visit.

IC 802**Exceptions from Informed Consent for Emergency Use of a Test Article
(21 CFR 50.23)****A. Waiver of Informed Consent Under Compassionate Use or on an Emergency Basis**

Please see also Human Research Protection Program: Policy and Procedure, No. 2, "Investigational Device Usage in Research & Development Service." **Note:** Even in an emergency situation, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing the four items outlined below. [21 CFR 50.23 (a)].

An exception under FDA regulations at 21 CFR 50.23 (a) permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article.
2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject and there is a medical emergency or urgency.
3. Time is not sufficient to obtain consent from the subject's legally authorized representative and there is a medical emergency or urgency.
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life and there is a medical emergency or urgency.

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required above in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. All of the documentation from the investigator and non-participating physician must be submitted to the IRB within 5 working days after the use of the test article. This reporting must not be construed as an approval for the emergency use by the IRB. (Note: This use without prospective IRB approval is not research, but medical treatment, and cannot be counted as research data.)

SC 901**Behavioral and Social Sciences Research**

This type of research often involves surveys, observational studies, personal interviews, or experimental designs involving exposure to some type of stimulus or intervention. This section discusses some additional IRB considerations.

A. Social and Psychological Harms

When evaluating behavioral and social science research, the IRB should carefully examine the research to determine the probability of risk of harm to subjects, especially with respect to social or psychological harm. This includes, but is not limited to the following:

1. The IRB should consider the potential for participants to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm.
2. The IRB should also consider the risks of criminal or civil liability or other risks that can result in serious social harms, such as damage to financial standing, employability, insurability, or reputation; stigmatization; and damage to social or family relationships.
3. If information is being collected on living individuals other than the primary "target" subjects the IRB should consider the risk of harm to those "non-target" individuals, as well. "Non-target" individuals may include members of the subject's family.

To mitigate such risks, the IRB should review the proposal for appropriate preventive protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in or affected by the research.

B. Privacy and Confidentiality Concerns

The use of confidential information is an essential element of much social and behavioral research. It is important to ensure that the methods used to identify potential research subjects or to gather information about subjects do not compromise the privacy of the individuals. In general, identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent of the subject. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research. However, there are circumstances that are exempt from the regulations, and circumstances in which the IRB may approve a waiver of the usual informed consent requirements.

It is also important to ensure that adequate measures are taken to protect individually identifiable private information once it has been collected to prevent a breach of confidentiality that could lead to a loss of privacy and potentially harm subjects.

The IRBs serve as the Privacy Boards for Research at the Portland VA Medical Center and abide by the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and the HRPP Policy & Procedure No. 6, located in Appendix N. The IRB recognizes the importance of protecting subject confidentiality, and carefully evaluate each protocol for the confidentiality measures taken.

C. Safeguarding Confidentiality

When information linked to individuals will be recorded as part of the research design, the IRB should ensure that adequate precautions should be taken to safeguard the confidentiality of the information. The more sensitive the data being collected, the more important it is for the researcher and the IRB to be familiar with techniques for protecting confidentiality. The IRB may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC). The CoC protects against the involuntary release of sensitive information about individual subjects for use in Federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings.

D. Research Involving Deception or Withholding of Information

Sometimes in psychological or educational research deception is necessary to prevent participant bias. When the IRB reviews research projects involving incomplete disclosure or deception, it must apply both common sense and sensitivity to the review.

Where deception is involved, the IRB needs to be satisfied that the deception is necessary and that, when appropriate, the subjects shall be debriefed. (Debriefing may be inappropriate, for example, when the debriefing itself would present an unreasonable risk of harm without a corresponding benefit.) The IRB should also make sure that the proposed subject population is suitable.

Deception can only be permitted where the IRB documents that a waiver of the usual informed consent requirements is justified under the criteria present in VA regulations and the Common Rule and 38 CFR 16.116(d). Specifically, the IRB must find and document that all four of the following criteria have been satisfied:

1. The research presents no more than minimal risk to subjects.
2. The waiver or alteration shall not adversely affect the rights and welfare of the subjects.
3. The research could not practicably be carried out without the waiver or alteration.
4. Where appropriate, the subjects shall be provided with additional pertinent information after participation.

In making the determination to approve the use of deception under a waiver of informed consent, the IRB should consider each criterion in turn, and document specifically (in the minutes of its meetings and/or in the IRB protocol file) how the proposed research satisfies that criterion.

SC 902

Research Using Data

Many studies combine characteristics of behavior and social research with characteristics of biomedical research. There are many interdisciplinary combinations of behavioral and medical research. These types of studies often use or create data repositories (banks). The following is guidance for the IRB when considering these types of studies.

A. Prospective Use of Existing Materials

Prospective studies are designed to observe outcomes or events (e.g., diseases, behavioral outcomes, or physiological responses) that occur subsequent to identifying the targeted group of subjects, proposing the study, and initiating the research.

Prospective studies using materials (data, documents or records) that will "exist" in the future because they will be collected for some purpose unrelated to the research (e.g., routine clinical care) do not qualify for **exemption** under VA regulations at 38CFR16.101 (b)(4) because the materials in these studies are not in existence at the time the study is proposed and initiated.

B. Retrospective Use of Existing Materials

Retrospective studies involve research conducted by reviewing materials (data, documents or records) collected in the past (e.g., medical records, school records, or employment records) and existing at the time the research is proposed and initiated.

1. Such research may be exempt under Department of Veterans Affairs (VA) regulations at 38CFR16.101 (b)(4) if the information is publicly available or if the information is recorded in such a manner that subjects cannot be identified, either directly or through identifiers linked to the subjects.
2. If not exempt, the IRB may review such research utilizing expedited procedures, provided that the research involves no more than minimal risk to subjects.
3. However, retrospective studies using existing materials occasionally entail significant, greater than minimal risks and require review by the convened IRB (e.g. where the research reveals previously undisclosed illegal drug use and the expedited review raised concerns about invasion of subjects' privacy and/or the adequacy of confidentiality protections proposed by the investigators).

C. Research Utilizing Large Existing Data Sets

The use of large, existing data sets, i.e. data that must be "on the shelf" at the time the protocol is initiated, requires IRB review when they contain individually-identifiable private information about individuals. In such cases, the IRB must determine whether the information can be used without additional informed consent from the subjects.

1. In making this determination, the IRB should first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the original terms of consent.

2. If this is not the case, then the IRB should consider whether it is permissible to waive the usual informed consent requirements in accordance with 38 CFR 16.116(d).
3. In other cases, the IRB may determine that the research can proceed only if the investigator obtains and uses "anonymized" data. Under this scenario, codes and other identifiers are permanently removed from the data set before the data are sent to the investigator, and the removal is accomplished in such a manner that neither the investigator nor the source maintaining the data set can re-establish subjects' identities.
4. An alternative to anonymizing data is to maintain the data set as a data repository under the guidelines established by the Office for Human Research Protections (OHRP) and VA.

D. Research Utilizing Data Banks (also called Repositories)

Human data repositories collect, store, and distribute individually-identifiable information about individual persons for research purposes.

Data Bank activities involve three components: (a) the **collectors** of data; (b) the **bank/repository** storage and data management center; and (c) the **recipient** investigators. Under a repository arrangement, the IRB formally oversees all elements of repository activity, setting the conditions for collection, secure storage, maintenance, and appropriate sharing of the data with external investigators. Specifically, the IRB determines the parameters for sharing data and/or tissues (which are identifiable within the repository) in a manner such that additional informed consent of subjects is, or is not, required.

Typically, these parameters may involve formal, written agreements between the investigator and the tissue repository stipulating conditions as follows:

1. The repository shall not release any identifiers to the investigator.
2. The investigator shall not attempt to recreate identifiers, identify subjects, or contact subjects.
3. The investigator shall use the data only for the purposes and research specified.
4. The investigator shall comply with any conditions determined by the repository IRB to be appropriate for the protection of subjects.

SC 903**Epidemiological Research**

Epidemiological research often makes use of sensitive, individually identifiable, private information (usually obtained from medical or other private records), and links this information with additional information obtained from other public or private records, such as employment, insurance, or police records. Epidemiological research may also combine historical research with survey and interview research. Epidemiological studies often present significant problems regarding both **privacy and confidentiality**.

1. The IRB must first consider privacy issues, and must satisfy itself that the research does not constitute an unwarranted invasion of the subjects' privacy. In doing so, the IRB shall seek to establish that the investigator has legitimate access to any individually-identifiable information that is to be utilized. For example, if State disease registry information is to be utilized, the IRB will need to examine State law relative to the legitimate release of such information for research.
2. Once the IRB's privacy concerns have been resolved, the IRB will examine mechanisms for maintaining the confidentiality of data collected. The IRB shall seek to establish that confidentiality protections are appropriate to the nature and sensitivity of the information that has been obtained. Confidentiality protections will be in accordance with HIPAA.
3. Because epidemiological research typically requires large numbers of subjects, investigators almost always request that the IRB waive the usual requirements for informed consent. To approve such a waiver in epidemiological research, the IRB must find and document that the criteria for a waiver of informed consent have been met (38 CFR 16.116(d)).

SC 904

Family History Research

Family history research is a common technique used in bio-social and bio-behavioral research. Family history research typically involves obtaining information from one family member about other family members (third parties).

1. It is important to recognize that the VA regulations at 38 CFR 16.102 (f)(2) include in the definition of human subject a living individual about whom an investigator obtains "identifiable private information." Thus, the family members (third party) identified and described by their family member may be human subjects under the regulations if the investigators obtain identifiable private information about them.
2. The IRB must determine whether family members (third parties) are human subjects in such research, and if so, consider the possible risks involved, and determine whether their informed consent is required or can be waived under the conditions specified at 38 CFR 16.116(d). There is not total consensus in the available guidance on this issue. OHRP representatives have advised that "third parties" about whom identifiable and private information is collected in the course of research are human subjects. Confidentiality is a major concern in determining if minimal risk is involved. The IRB can consider if informed consent from third parties can be waived in accordance with Section 45 CFR 116 (d) and if so, document that in the IRB minutes. In most cases waiver of consent may be appropriate.

SC 905

Research Involving Potentially Addictive Substances

Research involving potentially addictive substances often involves the use of what may be termed "abuse-liable" substances. Abuse-liable substances are pharmacological substances that have the potential for creating abusive dependency. Abuse-liable substances can include both legal and illicit drugs. The following are among the issues that the IRB should consider when reviewing research involving potentially addictive substances:

1. When this type of research is proposed, the IRB must consider the subjects' capacity to provide continuous informed consent, ensuring that subjects are competent and are not coerced.
2. If such research involves subjects that are institutionalized, the subjects' ability to exercise autonomy could be impaired.
3. The IRB must also consider the requirements for equitable selection of subjects and protections for maintaining confidentiality, as such a population may be at risk for being discriminated against, or over-selected.
4. The IRB must be sensitive to the ethical context of the research, in that there may be moral dilemmas associated with the use of placebos, or in cases where addicts are presented with alcohol and/or drugs.
5. It is critical that the IRB focus on the considerations of risk and benefits of such research.

SC 906

Research Involving PVAMC Employees, Students and Trainees

The IRB upholds the standards in approving research involving PVAMC employees, students and/or trainees. The IRB takes into consideration undue influence that an employee may experience as being approached for participating in a research project. The IRB ensures that no employees, students, or trainees feel obligated to participate in research in order to avoid loss of employment or privileges. Investigators, who would like to recruit VA employees for a research project, may be required to obtain approval from the local American Federation of Government Employees (AFGE).

SC 907

Human Fetal Tissue Transplantation Research

The PVAMC does not conduct research with human fetal tissue transplantation.

SC 908

Research Involving Deceased Persons

In the rare cases that such studies are proposed, the IRB will review such research projects involving deceased persons by evaluating the nature of the research and determining if consent of family members is necessary, or whether the body may be treated in the same manner as that of donated tissue. The IRB also ensures that appropriate confidentiality measures are in place.

Under HIPAA, investigators who propose research involving decedent's protected health information must complete the "Research on Decedent's Information Application." This application will be reviewed and approved by the IRB Chair(s), since the Common Rule does not cover research involving decedent's information. The investigators will be expected to adhere to the provisions of HIPAA. Additional information regarding research on decedent's information is detailed in the HRPP Policy and Procedure, No.6, located in Appendix N.

FD 1000

Investigational Drugs, Devices, and Biologics

The Food and Drug Administration (FDA) is a component of the U.S. Department of Health and Human Services (DHHS). The FDA's mission is to promote and protect the public health by helping safe and effective products reach the market, and then monitoring these products for continued safety while they are in use.

The FDA regulates clinical investigations (research) conducted on drugs, biologics, devices, diagnostics, and, in some cases, dietary supplements and food additives, hereinafter referred to as "FDA regulated test articles." All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor.

When an FDA regulated test article is used in research being done at the VA or funded by another federal agency, more than one set of regulations may apply. For example, clinical trials involving FDA regulated test articles that are supported by DHHS (e.g., the National Institutes of Health) fall under the jurisdiction of both the FDA and the DHHS Office for Human Research Protections (OHRP). Such trials must comply with the FDA and the DHHS human subject regulations as well as VA regulations and the Common Rule. Where regulations differ, the IRB should apply the stricter one.

For information regarding Investigational Devices, please refer to HRPP: Policy & Procedure No. 3, "Investigational Device Usage in Research & Development Service," in Appendix J.

The PVAMC Research Pharmacy is responsible for maintaining the written policies and procedures for the Research Pharmacy and the dispensing of investigational drugs.

A. FDA Requirements in Relation to VA, Common Rule, and DHHS Requirements

The human subject protection requirements found in FDA regulations are substantially the same as the VA and Common Rule requirements. However, there are important differences:

1. The FDA has different definitions for "human subject" and "clinical investigation (research)."

FDA regulations (21CFR56.102(e)) define a human subject as "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient."

FDA regulations (21CFR56.102(c)), defines clinical investigation as "...any experiment that involves a test article and one or more human subjects..." The FDA regulations further state that "...The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part."

The FDA definition of research in the Investigational New Drug (IND) regulations is as follows: "Clinical investigation" means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of

medical practice” (21CFR312.3(b)) Thus, under the FDA IND regulations, it is possible for one drug given to one person to be considered research.

2. FDA has neither an assurance mechanism nor files of IRB membership. Therefore, FDA does not require the IRB or institution to report changes in membership whereas HHS does require such notification.
3. Conditions for exemption, exception (21 CFR 50.23), and waiver (45 CFR 46.116(c) &(d) of IRB review and informed consent requirements differ.
4. FDA regulations require specific determinations for the IRB review of device studies (see HRPP: Policy & Procedure No. 2).
5. FDA regulations include specific requirements for reporting adverse events that are not found in VA regulations, the Common Rule, or DHHS regulations.
6. DHHS regulations include specific additional protections for pregnant women, fetuses, and human in vitro fertilization (Subpart B); prisoners (Subpart C) and children (Subpart D) that are not contained in the VA, and Common Rule requirements. In April 2001 FDA issued regulations to protect children in research (20 CFR 50 Subpart D). In April 2001 the VA Office of Research and Development issued Directive 2001-028, requiring a centralized waiver.

In addition to regulations governing human subject protection, the FDA also has regulations governing the use of investigational drugs (21 CFR 312) and devices (21 CFR 812).

B. Additional VA Requirements

VA policy (M-3, Part 1, Chapter 9) requires that all research comply with the VA human subject regulations, as well as with all applicable regulations and requirements regarding storage and security procedures for investigational agents. The following applies to studies using an investigational drug, an approved drug used for an unapproved indication or an approved drug used as a comparator in a study.

1. A VA Investigational Drug Information Record (VA Form 10-9012) must be completed by the principal investigator, submitted to the Research Service office and monitored by the Research and Development (R&D) Committee (M-3, Part 1, Chapter 9.15 b. (3)).
2. Upon approval of the research by the IRB and R&D Committee, a Report of Subcommittee on Human Studies (VA Form 10- 1223) must be forwarded to the investigator and the Pharmacy Service.

These 2 forms (10-9012 and 10-1223) are sent to the Pharmacy Service.

C. Research Involving Investigational FDA Regulated Test Articles

Please see also Human Research Protection Program, Policy and Procedure No.2 “Investigational Device Usage in Research & Development Service.” Medical products, such as drugs, biologics, and medical devices need to be proven safe and effective before the FDA can approve them for sale to and use by patients. FDA reviews the results of laboratory, animal and human clinical testing to determine if the product to be put on the market is safe and effective. New medical products that have not yet

been approved for marketing by the FDA require a special status so they can be legally shipped for the purpose of conducting clinical investigations to establish safety and efficacy.

1. The IND is an investigational new drug application and is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." Investigational new drug (or investigational drug) means a new drug or biological drug that is currently unapproved by the FDA for marketing is being used in a clinical investigation. An investigational drug must have an IND before it can be shipped.
2. An approved investigational device exemption (IDE) permits a device not approved by FDA to be shipped to conduct clinical investigations of that device. Not all investigational devices need an IDE.
3. With only a few exceptions, most clinical research being done on FDA regulated test articles with either an IND or IDE will need initial review at a convened IRB meeting.

D. Investigator and Sponsor Responsibilities

Under FDA regulations, the **investigator** in a clinical trial is responsible for the conduct of the study and for leading the team of individuals coordinating the study. These responsibilities include:

1. Obtaining IRB approval and promptly report to the IRB changes in the research activity and all unanticipated risk to human subjects;
2. Getting informed consent from each subject;
3. Following the investigational plan;
4. Complying fully with the regulations;
5. Protecting the rights, welfare and safety of the subjects;
6. Supervising the use and disposition of the test article;
7. Maintaining accurate, current and complete records; and
8. Disclosing relevant financial information.

The **sponsor** takes responsibility for initiating the clinical investigation, and holding the IND or IDE, but does not usually conduct the investigation. Although the sponsor is usually a pharmaceutical, biotech, or medical device company, an individual or group of individuals or medical center can also be considered a sponsor for an investigation. An investigator is referred to as the sponsor-investigator when the individual investigator is also the initiator of the clinical investigation. Some of the responsibilities of sponsors are:

1. Selecting qualified investigators;
2. Providing investigators with the information they need to conduct the investigation properly;

3. Ensuring proper monitoring of the investigation;
4. Monitoring an effective IND and IDE with respect to an investigator; and
5. Ensuring that the FDA and (for devices) any reviewing the IRB or (for drugs) all participating investigators are promptly informed of significant new information about an investigation.

E. Necessity of an Investigational New Drug (IND) Number from the FDA

(21 CFR 312.2 (b))

The IRB will take the following information into account when determining whether or not an investigational drug requires an investigational new drug number from the FDA.

A clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of 21 CFR 312.2 if all of the following apply, i.e., does not require an IND Number from the FDA:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
2. If the drug is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not indeed to support a significant change in the advertising for the product.
3. The investigation does not involve a route of administration or dosage or level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
4. The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7.

F. IRB Review of Medical Devices

Please see the Human Research Protection Program, Policy and Procedure No.2 “Investigational Device Usage in Research & Development Service,” in Appendix J.

G. Radiology Devices and Radioactive Materials

All studies involving Radiological devices or procedures are reviewed by the Radiation Safety Officer (RSO), who is a member of one IRB. Studies from the other IRB which include a radiation component are also sent to the RSO for review. The Radiation Safety Officer assures that the use of radioactivity and the conduct of procedures are appropriate.

H. AEs and Reporting Requirements

Some requirements for reporting AEs are the same, regardless of what sort of test article is used (e.g. a drug or a device). FDA, VA, and DHHS regulations require **prompt** reporting to the IRB, FDA,

OHRP, and the Office of Research Oversight (ORO) of any unanticipated problems involving risks to human subjects and others.

1. FDA interprets "any unanticipated problems involving risks to human subjects" to mean "...an unexpected adverse experience that is not listed in the labeling for the test article. -including an event listed in the labeling ... that differs ... because of greater specificity or severity" (FR 28027).
2. FDA interprets "...and others" to mean "...persons who are participating in clinical trials under the same or similar protocols or who may be affected by products or procedures developed in those trials" (FR 28027).

AE information submitted to the sponsor by the investigator should also be submitted to the IRB in accordance with the IRB PVAMC AE reporting policy. In addition to providing **prompt** written notification to relevant Federal agencies, including ORO, FDA, and OHRP, of any unanticipated problems involving risks to subjects or others, the IRB should also report the resolution of those problems.

I. AEs and Reporting Requirements – INDs

FDA IND regulations (for both drugs and biologics) have requirements related to the reporting of adverse events.

1. **Investigator Reports to Sponsor:** FDA IND regulations require that the investigator report promptly to the sponsor any "adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately" (21 CFR 312.64(b)).
2. **Sponsor Reports to FDA and Investigators:** FDA IND regulations require that the sponsor notify the FDA and all participating investigators of any adverse experience associated with the use of the drug or biologic that is **both** serious **and** unexpected as soon as possible but **in no event later than 15 calendar days after the sponsor determines it to be reportable**, 21CFR312.32(c)(B).

The FDA should be notified by telephone, facsimile, or in writing as soon as possible but **in no event later than 7 calendar days of the sponsor's receipt of the information of any unexpected fatal or life-threatening experience.**

"Serious adverse drug experience" is defined as "any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect," (21 CFR 312.32(a)).,

J. AEs and Reporting Requirements – IDEs

FDA IDE (device) reporting requirements are similar but not exactly the same as for drugs and biologics, 21CFR812.50.

1. **Investigator to Sponsor:** FDA IDE regulations require that the investigator notify the sponsor and the IRB of any unanticipated adverse device effect **within 10 days of discovery**.
2. **Sponsor to FDA, Investigator, and IRB.** The sponsor is required to evaluate the event and report it to the FDA, to all participating investigators, and to all reviewing the IRB **within 10 working days of the sponsor's receipt of the information**.

K. "Off-label" (Unapproved) Use of FDA-Regulated Products in Medical Practice

The FDA approves the sale, use, and labeling of a product for specific indications (the reason the product is being used - a disease, condition, as a diagnostic tool, etc.). "Off-label" or unapproved use is when the product is used in a way or on a population different from that for which it was approved. The IND regulations do not apply to the use of marketed drugs for unlabeled indications in the practice of medicine (21 CFR 312.2(d)).

L. "Off-label" (Unapproved) Use of FDA Regulated Products in Research

Good medical practice and the best interests of the patient require that physicians use legally available, marketed drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not included in the approved labeling (i.e., off-label), they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.

The off-label use of a marketed drug or biologic in **research** does require IRB review, informed consent and, under some circumstances, may require an IND. To be exempt from the requirements of the IND regulations, all of the following must apply (note that this includes the requirement of IRB review and informed consent):

1. The investigation is not intended to support of a new indication for use nor any other significant change in the labeling for the drug;
2. The investigation is not intended to support a significant change in the advertising for the product;
3. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
4. The investigation is conducted in compliance with the requirements for institutional review board review and informed consent; and
5. The investigation is conducted in compliance with the FDA regulations on promoting and charging for investigational drugs (21 CFR 312.7).

Use of an off-label marketed product in research intended to support **a new indication for use, change in labeling or advertising** requires IRB review, informed consent and submission of an IND.

Using an off-label marketed product in research involving a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the

acceptability of the risks) associated with its use requires IRB review, informed consent and may also require submission of an IND.

M. **Expanded Access to Investigational Drugs**

Investigational products are sometimes used for treatment of serious or life-threatening conditions either for a single subject or for a group of subjects. The procedures that have evolved for an investigational new drug (IND) used for these purposes reflect the recognition by the FDA that, when no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval (21 CFR 312.34, 312.35, and 312.83).

1. **Open Label Protocol or Open Protocol IND**

These are usually uncontrolled studies, carried out to obtain additional safety data (*Phase III studies*). They are typically used when the controlled trial has ended and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective IRB review and informed consent.

2. **Treatment IND**

The treatment IND (21 CFR 312.34 and 312.35) is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug. Four requirements must be satisfied before a treatment IND can be issued:

- (1) The drug must be intended to treat a serious or immediately life threatening disease;
- (2) There must be no satisfactory alternative treatment available;
- (3) The drug must already be under investigation or the drug trials must have been completed; and
- (4) The trial sponsor must be actively pursuing marketing approval.
- (5) Treatment IND studies require prospective IRB review and informed consent.

3. **Parallel Track Studies.** FDA also permits wider access to promising new drugs for HIV/AIDS related diseases under a "separate access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. These so-called "parallel track" studies require prospective IRB review and informed consent.

N. **Expanded Access to Investigational Devices**

Please see also Human Research Protection Program, Policy and Procedure No.2 "Investigational Device Usage in Research & Development Service," in Appendix J. According to statute and FDA

regulations, an unapproved medical device may normally only be used in human subjects when the device is under clinical investigation and when used by investigators participating in the clinical trial. FDA recognizes, however, that there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient, to prevent irreversible morbidity or to help a patient suffering from a serious disease or condition for which there exists no alternative therapy. Four main mechanisms are utilized by FDA to make unapproved devices available to patients/physicians faced with circumstances such as those described above. These mechanisms are consistent with the Expanded Access provisions of the FDA Modernization Act of 1997 (Section 561 of the Federal Food, Drug, and Cosmetic Act). The sponsor must agree and FDA must approve the use. Under most circumstances such studies require IRB review and informed consent.

1. **Emergency Use** - Regulatory Authority: 50 FR 42866 and 21 CFR 812.35(a) and “Guidance for the Emergency Use of Unapproved Medical Devices.”
Criteria for use under this expanded access mechanism includes that the subject must 1) have a life-threatening condition; 2) no alternative is available and 3) no time to obtain FDA approval of the device. This may be used before or after initiation of a clinical trial. Access is limited to a few patients. FDA approval of use of the investigational device is not required prior to use. After the device is used a report should be submitted to the FDA. The necessary patient protection measures that must be followed include: 1) independent assessment by an uninvolved doctor; 2) IRB chairperson’s concurrence; 3) institutional clearance from the Chief of Staff or his designee; 4) informed consent.
2. **Treatment Use/IDE** – Regulatory Authority: **21 CFR 812.36.**
Criteria for use under this expanded access mechanism includes that the subject must 1) have a life-threatening condition or serious disease; 2) no alternative available and 3) the device is being used in a controlled clinical trial and 4) the sponsor is pursuing marketing approval. This may be used only during a clinical trial. Access is available widely, depending on the patient and physician needs. FDA approval of use of the investigational device is required prior to use. FDA approval is obtained via a Treatment Investigational Device Exemption (IDE) supplement with: 1) intended Use, protocol, and patient selection criteria; 2) rationale for treatment use; 3) methods used to evaluate devices use and minimize risks; 4) monitoring plan; 5) summary of safety and efficacy data; 6) instructions for use and device labeling; 7) commitment to patient protection; 8) investigator agreement; and 9) the price if it will be sold. The necessary patient protection measures that must be followed include: 1) IRB approval and 2) informed consent.
3. **Continued Access to Investigational Devices** – Regulatory Authority: “Continued Access to Investigational Devices During PMA Preparation and Review” and ODE Blue Book IDE Memorandum #D96-1.
This mechanism allows access to a device while a marketing application is being prepared and reviewed, and can be used to collect additional evidence of safety and effectiveness, as well as to address new questions regarding the investigational device, such as labeling claims.

Criteria for use under this continued access mechanism includes that there must be: 1) a public health need for the device and 2) preliminary evidence that the device is effective and there are no significant safety concerns. This may be used only after the completion of a clinical trial. The number of patients that may be treated is the same rate of enrollment as

study. FDA approval of use of the investigational device is required prior to use. FDA approval is obtained via a Investigational Device Exemption (IDE) supplement with: 1) justification for extended study; 2) summary of safety and efficacy data and risks posed by the device; 3) proposed enrollment rate; 4) clinical protocol; and 5) progress towards marketing approval. The necessary patient protection measures that must be followed include: 1) IRB approval and 2) informed consent.

4. **Compassionate Use** – Regulatory Authority: 21 CFR 812.35(a)

Criteria for use under this expanded access mechanism includes that the subject must have a serious condition/disease with no alternative intervention available. Compassionate use may be used only during the conduct of a clinical trial. Access is limited to an individual patient or a small group of patients. FDA approval of use of the investigational device is required prior to use. FDA approval is obtained via a Investigational Device Exemption (IDE) supplement with: 1) explanation of circumstances constituting need for the device; 2) reasons alternatives are not acceptable; 3) deviations from protocol, if any; and 4) patient protection measures. The necessary patient protection measures that must be followed include: 1) independent assessment by an uninvolved doctor; 2) IRB chairperson's concurrence; 3) institutional clearance from the Chief of Staff or his designee; 4) informed consent.

Stated in the U.S. Department of Health & Human Services, Guidance on IDE Policies and Procedures (p. 18) is "As a matter of practice, FDA has expanded the criteria of "life-threatening condition" to include serious diseases or conditions such as sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity. This is consistent with the new law."

O. Gene Transfer Research

Gene transfer involves the administration of genetic material to alter the biological properties of living cells for therapeutic use. Gene transfer activities in humans are investigational and are regulated by the both the FDA and the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA).

1. FDA regulations require the submission of an IND for human gene transfer research through the FDA Center for Biologics.
2. DHHS regulations specify that no individual may be enrolled in human gene transfer research until review has been completed by the NIH Recombinant DNA Advisory Committee (RAC), local Institutional Biosafety Committee (IBC) approval has been obtained, local IRB approval has been obtained, and the investigator has obtained all other regulatory authorizations from the subject (FR 196, October 10, 2000).
3. While the RAC is advisory to the Director of the NIH, compliance with RACs guidelines is mandatory for all investigators at institutions that receive NIH funds for research involving recombinant DNA.

P. Emergency Use of a Test Article Without IRB Review

Please see also Human Research Protection Program: Policy and Procedure No. 2, "Investigational Device Usage in Research & Development Service," in Appendix K for information regarding the emergency use of investigational devices.

An exemption under FDA regulations at 21 CFR 56.104(c) permits the emergency use of an investigational drug, or biologic on a one-time basis per institution without IRB review and approval. The first three of the following conditions must be met for this type of emergency use:

1. A human subject is in a life-threatening situation.
2. No standard acceptable treatment is available.
3. There is insufficient time to obtain IRB approval.
4. The emergency use must be reported to the IRB within five working days. This reporting must not be construed as an approval for the emergency use by the IRB.
- e. Ordinarily, the investigator must obtain the informed consent of the subject for such an emergency use, except as described below.

VA policy M-3, Part 1, Chapter 9.15(f)(2)(a) requires separate authorization from the Chief Medical Director for patients outside a research protocol for each such emergency use of a test **article without IRB review**, as well as the filing of VA Form 10-9012, Investigational Drug Information Record with the Pharmacy Service.

Q. “Compassionate” or “Humanitarian” Use of a Test Article

Questions frequently arise regarding "compassionate" or "humanitarian" use of a test article. "Compassionate use" and "humanitarian use" are not terms that appear in the VA, or DHHS regulations or the Common Rule. "Compassionate use" and "humanitarian use" are often meant to refer to the emergency use situations discussed above.

R. Humanitarian Use Device (HUD)

The FDA defines humanitarian use device: “is a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or is manifested in fewer than 4,000 individuals in the United States per year.” U.S. Food and Drug Administration – Center for Devices and Radiological Health, Humanitarian Device Exemption (HDE) Regulation Questions and Answers: Final Guidance for Industry, July 12, 2001.

A HUD requires a Humanitarian Device Exemption (HDE) for the FDA. A HDE is an application that is similar to a pre-market approval (PMA) application, but exempt from the effectiveness requirements of a PMA. An approved HDE authorizes marketing of a Humanitarian Use Device (HUD).

FDA regulations (21 CFR 814.124(a)) require the IRB to conduct a full board review of a HUD prior to its use, except in emergency situations in which the physician determines that approval cannot be obtained in time to prevent serious harm or death to the patient. An investigator who would like to use a HUD, must forward a letter of request to the IRB. Effective January 2003, the clinician/investigator must also submit the Proposed Project Questionnaire (PPQ), protocol and any other additional information requested. The convened full board IRB will review and make a determination of the use of the HUD at the PVAMC. However, the IRB does not have to approve individual uses of the HUD if it is within the FDA approved indication.

The HDE regulations do not require the use of informed consent because the HDE provides for marketing approval and so use of the HUD does not constitute research or an investigation, which

would normally require informed consent. In these cases, the clinician/investigator must provide a copy of the clinical consent to be used to the IRB. However, if the HUD is the subject of a clinical investigation (the HDE holder is collecting safety and effectiveness data to support a PMA under the approved HDE) IRB approval and informed consent are required (21 CFR Parts 56 and 50).

If the IRB approves the use of the HUD, the HUD will be reviewed on an annual basis by the IRB. The continuing review of the HUD may be performed under an expedited process. The HUD will be tracked in the MIRB database.

The HUD Review Process flowchart may be found in Appendix T.

S. Off-label Emergency Use of a Humanitarian Use Device (HUD)

Reference: Humanitarian Device Exemption (HDE) Regulations: Questions and Answers; Final Guidance for Industry, Issued July 12, 2001. <http://www.fda.gov/cdrh/ode/guidance/1381.html>

HUDs may be used off-label in an emergency situation, but certain patient protection measures should be followed before the use occurs. Because IRB review and approval is required before a HUD is used within its approved labeling, a HUD should not be used outside of its approved labeling without similar restrictions. That is, in an emergency situation, a HUD may be used off-label to save the life or protect the physical well-being of a patient, but the physician and HDE holder should follow the emergency use procedures governing such use of unapproved devices. According to this policy, before the device is used, if possible, the physician should obtain the IRB chairperson's concurrence, informed consent from the patient or his/her legal representative, and an independent assessment by an uninvolved physician. In addition, authorization from the HDE holder would be needed before the emergency use of the HUD. After the emergency use occurs, the physician should submit a follow-up report on the patient's condition and information regarding the patient protection measures to the HDE holder, who would then submit this report as an amendment to the HDE.

The physician should follow the procedures outlined in HRPP Policy & Procedure No. 2, "Investigational Device Usage in Research & Development Service," Section 5.c.

R. Requirements for Planned Emergency Research (21CFR50.24)

The PVAMC may not review and conduct planned emergency research, according to the VA Office of Research Oversight (ORO), formally known as the Office of Research Compliance & Assurance (ORCA). Please see Appendix U for the related documentation.